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## SURGICAL TREATMENT OF TENSION CAVITIES IN PULMONARY TUBERCULOSIS<sup>1,2</sup>

HERBERT C. MAIER

Collapse therapy has proved efficacious in closing a large percentage of tuberculous pulmonary cavities. It has been evident for several years, however, that some do not respond readily to collapse measures. Although the size of the cavity is of some importance, other characteristics are of perhaps greater significance. The intracavitary pressure plays an important rôle in determining the response to collapse therapy. Therefore tension cavities present a major problem in the treatment of pulmonary tuberculosis and account for a large number of the failures of pneumothorax and thoracoplasty. The pathological physiology of tension cavities will first be discussed briefly because rational therapy depends on an understanding of these fundamentals. The various types of surgical treatment for tension cavities will then be considered.

When caseation necrosis with excavation occurs in pulmonary tuberculosis, usually a more or less spherical defect in the lung occurs due to the elastic properties of the adjacent parenchyma. A small area of caseation may be followed within a week or two by a cavity of considerably greater size as demonstrated by serial roentgenograms. Thus, the size of the cavity does not indicate an equivalent area of pulmonary destruction. Although progressive peripheral caseation may be a factor in the enlargement of the tuberculous cavity, mechanical distension may also play an important rôle. The type of bronchial communication determines the facility with which air may enter or leave the cavity. The pressure within a pulmonary cavity may be either negative, atmospheric, or positive. A negative or an atmospheric pressure does not offer any obstacle to collapse therapy. A positive intracavitary pressure, however, may seriously interfere with closure by pneumothorax or thoracoplasty.

A positive pressure may develop due to a partial obstruction in the draining bronchus. The obstructive factor in the bronchial lumen may be either due to the involvement of the wall by a tuberculous process, the presence of tenacious secretion within the bronchial lumen or, perhaps, to spasm of the bronchial wall. Because the bronchus draining a tension cavity is often of small calibre, a slight alteration in the diameter of the bronchus may be of decided importance. As the bronchial lumen is normally larger during inspiration than during expiration, a check-valve mechanism may be produced in the draining bronchus. By this means, air can enter the tuberculous cavity during inspiration, but only a portion of the air can again escape during expiration. If there is a sudden increase in intrabronchial pressure, such as occurs in coughing, air may be forced into the cavity. This trapped air may then only escape intermittently. Although local factors in the draining bronchus are thought to be the cause of the

<sup>1</sup> From the Surgical Service of Triboro Hospital, Jamaica, New York.

<sup>2</sup> Presented before the Medical Section at the 40th annual meeting of the National Tuberculosis Association, Chicago, Illinois, May 11, 1944.

development of tension cavities, the frequent occurrence of multiple tension cavities in the same patient raises the question of some systemic influence. Whether this is due to some diffuse alteration in the bronchial wall or whether an element of spasm plays a rôle can only be conjectured at this time.

A large tension cavity may represent a defect in the lung which has been produced by a relatively small area of caseation necrosis with liquefaction. This is then inflated to large size by the trapping of air within the cavity because of the check-valve mechanism in the draining bronchus. Such cavities may therefore vary greatly in size over short periods of time. In some instances there is little change over a period of months or even years; but should an alteration in the check-valve mechanism of the draining bronchus occur, the size of the cavity may change rapidly. If the draining bronchus becomes completely obstructed, the air trapped within the pulmonary cavity will be absorbed and a negative rather than a positive pressure within the cavity will result. Marked shrinkage or complete obliteration of the cavity may then follow. If the check-valve mechanism of the draining bronchus is replaced by a free bronchial communication on inspiration and expiration, the positive pressure in the cavity will disappear. Under these circumstances, there will tend to be a reduction in its size, although usually not closure.

In many cases of cavitation in pulmonary tuberculosis there may be a difference of opinion concerning the recognition of a tension cavity on the basis of the roentgenogram alone. In other instances the behavior of the cavity over a period of time, as indicated by serial roentgenography, may conclusively demonstrate the pressure characteristics of the cavity. Although occasional observations of pressure readings of tuberculous cavities have been reported in the literature for a number of years, it is only recently that detailed observations of pressure readings on intrapulmonary cavities have been made. Eloesser (2), and Brunn and his coworkers (1) have published interesting observations on intracavitary readings in pulmonary tuberculosis. Riggins and Gearhart (3) made studies of intracavitary pressures. In some cases the same cavity was studied on a number of occasions over a considerable period of time. They have shown that, whereas a positive intracavitary pressure may exist at one time, the pressure may be less positive, atmospheric or even negative at another time. These alterations may occur spontaneously or be associated with collapse therapy or intracavitary drainage. As previously mentioned, the changes in the intracavitary pressure are secondary to alterations in the bronchial communication.

Until recently, needling of tuberculous cavities was thought to carry considerable hazard. By a careful technique, however, it has been shown that this procedure can be carried out with relatively little risk. Vineberg and Kunstler (4) recently reported 150 instances of needling of cavities in 62 cases. No ill effects and no complications occurred; that is, all needlings were accomplished without development of air embolism, empyema or gross hemorrhage. It should be emphasized that these good results can only be obtained if meticulous technique in needling is employed. Moreover, the introduction of any material

into the tuberculous cavity such as lipiodol would seem to increase the hazard. The injected material, mixed with secretion, may escape through the bronchial communication and thus occasionally cause a bronchogenic spread of the tuberculosis.

The behavior of tension cavities is unpredictable. Although it is known that this type of cavity is an important cause of failure of collapse therapy in pulmonary tuberculosis, such a cavity may nevertheless, at times, respond well to collapse treatment. Riggins and Gearhart (3) have determined the intracavitary pressure in cases which were later subjected to various types of therapy. In a few instances even a huge tension cavity disappeared spontaneously without any therapy other than bed-rest. A similar sequence of events has occurred occasionally in previous years when diaphragmatic paralysis was employed even for large cavities. The disappearance of a large cavity following either bed-rest alone or after diaphragmatic paralysis cannot be considered as necessarily due to the type of therapy given. It seems more probable that a chance alteration in the bronchial communication of the cavity, which may or may not have been influenced by the general or local rest treatment, caused the dramatic result. Moreover, similar spontaneous cavity closure may occur without any treatment whatsoever.

Tension cavities respond better to thoracoplasty than to pneumothorax therapy. This difference in result is not due to a difference in the degree of collapse obtained by the two methods of treatment. A balloon cavity remaining in a lung almost completely collapsed by pneumothorax may later be closed by a thoracoplasty. This result may be obtained although the thoracoplastic collapse is less complete than that previously accomplished by pneumothorax. It is therefore evident that the degree of collapse is not necessarily the deciding feature. The immobility of the thoracic cage with practical elimination of lung motion which follows extensive thoracoplasty may be an important factor. Because of the lack of mobility of the lung and bronchial tree under thoracoplasty, there may be a greater tendency to more complete blockage of the bronchus. In a number of cases of tension cavities subjected to thoracoplasty, I have noted a rising fluid level within the cavity. This indicated further impairment of bronchial drainage. In some such instances the site of the cavity was later replaced by a uniform opacity on the roentgenogram. Undoubtedly in these cases the cavity became filled with inspissated material rather than closed by apposition of its walls. The sputum might become negative, associated with the disappearance of the highlight on the roentgenogram. This conversion of sputum again was merely due to complete obstruction to cavitory drainage.

When a thoracoplasty is performed over a tension cavity it is not unusual to note persistence of the cavity immediately following conclusion of the series of operations. What at first seems to be a failure of thoracoplasty may some months later appear to be a satisfactory therapeutic result because of cavity closure under thoracoplasty. Although in the past closure of tension cavities under the thoracoplastic collapse has been attributed to contraction of fibrous



tissue within the lung, this seems to be an unsatisfactory explanation. Again the obstruction of the draining bronchus would seem to be the deciding feature.

Tension cavities subjected to pneumothorax therapy frequently enlarge as the lung is collapsed. Conversely, a large tension cavity in a well collapsed lung may become much smaller or disappear when the pneumothorax is abandoned. It has long been recognized that if pneumothorax therapy failed to accomplish cavity closure the percentage of cavity closure by later thoracoplasty was greater if the lung was first reexpanded before thoracoplasty was performed. If a markedly negative intrapleural pressure exists during pneumothorax therapy, it is readily understandable that the pressure gradient between the inside of the cavity and the pleural space would favor enlargement of a thin-walled cavity. Occasionally a positive pressure pneumothorax will temporarily compress the tension cavity. Vineberg and Kunstler (4) advocated routine needling of tuberculous cavities over 2.5 cm. in size. If a tension cavity was proved to exist, decompression by intracavitary suction drainage was considered indicated. A preliminary stage of thoracoplasty to remove the ribs in the area in which the catheter was to be introduced was first carried out. Then the catheter was introduced and intracavitary suction maintained. Later the thoracoplastic procedure was completed.

Although it is known that tension cavities are responsible for a considerable percentage of the therapeutic failures by thoracoplasty, the presence of a tension cavity does not necessarily mean that thoracoplasty will fail to close it. I am unaware of any series of cases of tension cavities treated either by pneumothorax or thoracoplasty in which both early and late results have been evaluated. Not infrequently an early, apparently excellent therapeutic result may prove to be a failure one or more years later. We have seen cavities which apparently closed on reexpansion of an unsuccessful pneumothorax, reopen at a later date. In such a case the late failure might be ascribed to the fact that the lung was reexpanded. Nevertheless, a similar occurrence has been noted under thoracoplasty. The cavity which at one time was closed may later reopen to large size in spite of a good thoracoplastic collapse. Therefore, in addition to the early results of collapse therapy for tension cavities being unsatisfactory, it must also be realized that the late results may be even less satisfactory.

Theoretically, it might seem most logical to treat tension cavities by decompression and later follow with thoracoplastic collapse. Several objections to this program must be mentioned. Even prolonged intracavitary suction drainage does not necessarily alter the condition of the draining bronchus of the cavity. Therefore, the possibility remains that at any time the cavity may reopen and again assume pressure characteristics. The Monaldi procedure may result in apparent closure of the cavity with conversion of the sputum, but even after subsequent thoracoplasty, performed to maintain closure, the cavity may reopen to large size. As far as I know, the literature does not contain any large series of cases in which intracavitary suction drainage was followed by thoracoplasty and the final results evaluated. Unless the reports limit the discussion of final results to cases in which all wounds and fistulae are closed, the program of treat-

ment cannot be completely evaluated, even as far as early results are concerned. Moreover, intracavitary suction drainage has been in use too short a time to permit evaluation of its late results in the early apparently successful cases.

Another objection which may be advanced against the routine application of intracavitary suction drainage prior to thoracoplasty, whenever an intracavitary reading has demonstrated the presence of a tension cavity, is the considerable percentage of cases which are thus needlessly subjected to a long period of therapy prior to thoracoplasty. In a considerable percentage of cases in which a Monaldi drainage has been successful when followed by thoracoplasty, the question arises whether the thoracoplasty alone might not have yielded a similar result.

When a thoracoplasty has failed to close a tension cavity, a secondary drainage of the cavity may be considered. The collapsed state of the pericavitary portion of the lung, however, may influence the response to suction drainage. If the adjacent pulmonary tissue has been collapsed by thoracoplasty for a considerable period of time, the possibility of reinflation and filling in the site of cavitation is reduced. In my experience, considerable difficulty has been encountered in obtaining cavity closure and complete wound healing following secondary cavernostomy after thoracoplasty.

If the pulmonary tuberculosis is limited chiefly to one lobe of the lung in which the tension cavity is located, the feasibility of pulmonary lobectomy must be considered. Although such a therapeutic program could hardly have been deemed advisable a few years ago, the situation is now somewhat different. The technique of lobectomy employed until the past few years involved leaving a stump of pulmonary tissue at the hilum. This residual pulmonary tissue usually contained tuberculous foci which were traumatized in the course of the operative procedure. Moreover, at that time the incidence of bronchial fistula after lobectomy performed for nontuberculous lesions was high. Therefore, lobectomy and pneumonectomy in the presence of active tuberculosis was regarded as an extremely hazardous procedure. Whereas these same potential dangers still exist to-day, refinements in surgical technique now permit in many cases a clean and meticulous surgical dissection of the individual pulmonary lobes. Therefore, at the present time, it is possible under ideal circumstances to perform pulmonary resection for active pulmonary tuberculosis with a reasonable fatality rate and only moderate danger of postoperative bronchial fistula and empyema. Recent advances in anesthesiology have permitted this meticulous and painstaking type of operative intervention and have lessened the dangers of tuberculous spread during operation. Therefore, at this time, it is appropriate to consider the treatment of tension cavities by pulmonary resection.

I have performed 16 lobectomies by hilar dissection for pulmonary tuberculosis in patients with positive sputum. In half of the cases a tension cavity was the indication for pulmonary resection. Ten patients had an entirely uncomplicated postoperative course. In 3 patients a previously existing lesion in the contralateral lung showed a transient perifocal flare-up. One of these cleared within a week. In the 2 patients in whom the contralateral reactivation was

more prolonged, both had sufficient disease in the contralateral lung to contraindicate thoracoplasty. Only 2 empyemata occurred, one of which was tuberculous while the other was pyogenic. A transient bronchial fistula was present in only the 2 empyema cases. There was one fatality in the entire series; death occurred a month following operation due to a contralateral tuberculous spread. At this time, all except 2 of the patients have a negative sputum, but in one additional case the operation is too recent to evaluate the sputum findings. To date 2 late complications have arisen. One patient, who left the hospital against advice five weeks after lobectomy and resumed a very active life, returned a few months later with reactivation in the lower lobe following a lobectomy of the left upper lobe. Another patient had a contralateral pleurisy several months following lobectomy, but this has since cleared.

I have performed 2 pneumonectomies for tension cavities. In one case even a revision thoracoplasty had failed to close the cavity. The other patient had failed to obtain cavity closure by pneumothorax. Both patients had an uneventful postoperative course.

The recent results of pulmonary resection in the treatment of tension cavity have been encouraging. Considerably more experience and a more prolonged follow-up will be necessary before the procedure can be properly evaluated. Moreover, pulmonary resection for tuberculosis requires a surgical set-up which is available in only a limited number of hospitals at this time.

#### SUMMARY

The pathological physiology of tension cavities has been briefly discussed. The advantages and disadvantages of various surgical procedures in the management of pressure cavities have been considered. The results of pulmonary resection are presented.

#### SUMARIO

Discútese aquí sucintamente la patofisiología de las cavernas de tensión y las ventajas y desventajas de varios procedimientos quirúrgicos en el tratamiento de las mismas, presentándose a la vez los resultados de la resección pulmonar.

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## TREATMENT OF INSUFFLATED CAVITIES<sup>1</sup>

LEO ELOESSER,<sup>2</sup> W. L. ROGERS<sup>2</sup> AND SIDNEY J. SHIPMAN<sup>2</sup>

Study of bronchial pathology and of the rôle played by the communicating bronchus in the formation of tuberculous cavities has led to attempts at formulating indications for variations in treatment of various kinds of cavities. It is unnecessary again to review the difficulties encountered in closure of cavities if all their varieties are subjected to a single routine collapse procedure. One of us (S. J. S.) has called attention to the inefficacy of pneumothorax in the collapse of insufflated cavities, another (L. E.) has pointed out that a study of intracavitary pressure by needling and manometry may guide us to one or another form of collapse or compression manoeuvres. It is not reasonable to try to collapse an insufflated cavity, the content of which is under positive pressure, by removing the surrounding ribs; some method which abolishes or counteracts the insufflating mechanism would seem more logical; if this is done the cavity should tend to collapse by itself. It would seem reasonable to do this by opening or draining the cavity to the outside, thus reducing intracavitary pressure to zero. However, incision and drainage of tuberculous cavities has been tried repeatedly only to be abandoned. This method is the earliest one of surgical treatment, but it has been fraught with so many dangers and difficulties that none of the countless surgeons who has attempted it has remained faithful to it as a standard method of surgical attack.

A pulmonary cavity is unlike an abscess in other organs or tissues; unlike other abscesses, both tuberculous and nontuberculous, it does not break spontaneously to the outside; moreover, once opened widely the surrounding lung continues to retract, so that what may have been a small cavity originally, soon becomes a huge one. A small cavity that may have been easy to deal with soon retracts to a huge cavern with a latticed wall pierced by many bronchial fistulae; a vast hollow, extremely difficult if not impossible to close. In order to counteract this irresistible tendency to shrink, it would seem prudent, then, not to open tuberculous cavities widely, if they are to be opened at all, but rather to drain their septic contents, if surgical operation has drainage for its object, or to deflate them, if indication for opening lies in deflation, through a small opening, applying measures at the same time to prevent retraction from gaining the upper hand. These measures may consist in external suction or some other device designed to limit the effect of external atmospheric pressure while still maintaining drainage; some device, in short, designed to keep the cavity under more or less constant negative pressure. External suction by means of a drainage tube connected to gravity bottles or a pump offers notorious technical difficulties. Besides, there is a more or less constant air-leak through the bronchus that connects with the cavity, which calls for endless supervision and adjustment of the suction

<sup>1</sup> Presented before the Medical Section at the 40th annual meeting of the National Tuberculosis Association, Chicago, Illinois, May 11, 1944.

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apparatus if it is to be really effective. For, in order to have the apparatus do what it is intended to, it must suck harder and faster than the bronchial leak admits air. In order to circumvent some of these difficulties a skin-flap was used for drainage. The skin-flap had proved its usefulness in draining empyemata and nontuberculous lung abscesses; attached to the pleura of an empyema or to the wall of an abscess it really does keep the pleura or the abscess under negative pressure, making escape of air or fluid easy, but entrance of atmospheric air difficult, by acting as a one-way valve. A *sine qua non*, however, for this valve action is that the empyema or the abscess have no bronchial connection, or at any rate a small one. In the presence of a larger bronchial fistula, which admits air to the pleura or the abscess freely, the flap will not produce negative pressure—this not only in theory, but in fact. However, as insufflated cavities or abscesses rarely if ever have a wide communicating bronchus, this difficulty has not proved troublesome in practice. In order to prevent the flap from being blown out from the cavity by pressure from the bronchial opening we have done the operation in two stages, a device recommended by Rogers.

The procedure may be undertaken either as a primary one or secondarily for residual cavities following thoracoplasty. We have used it as a secondary operation; in only one case was it used without previous thoracoplasty, or, in lower lobe cavities, without phrenic interruption.

The technique is simple. The cavity should be localized accurately and the route of access plotted before outlining the flap. Access may be anterior, lateral or posterior; the lateral route is preferred when feasible, the anterior one is the least desirable. The lateral (axillary) approach has several advantages. There are no large muscle masses to be traversed; the draining sinus is inconspicuous and covered by the arm; drainage is dependent and efficacious. Anterior flaps are hard to handle; the openings tend to enlarge, to ulcerate and to form sub-pectoral abscesses; drainage, with the patient recumbent or nearly so, is insufficient. In the posterior approach the flap has to be led across large masses of muscle; if the skin over the scapula is used, scapular movement is prone to pull the flap out of place. Whatever site is chosen, the base of the flap lies over the rib which is to be resected; the length of the flap is determined by estimating the distance between the skin at the base of the flap and the cavity wall. The U-shaped flap itself runs at right angles to the rib. The skin and subcutis are injected with procain, the flap is outlined with a U-shaped incision and lifted up; it consists of skin and subcutis only. The muscles and intercostal tissues are infiltrated with procain, the muscles are separated and the rib overlying the lower border of the cavity is resected together with its periosteum. In making the resection the raspatory is not used; the rib is isolated by passing a galvano-cautery or a dissecting current along its upper and lower edges, or, if neither of these instruments are at hand, by severing the intercostal muscle attachments with scissors. About two inches or more of the rib are removed. The edges of the flap are fastened to the pleura with two fine sutures taken at a suitable distance from its tip, a distance great enough to allow the tip to be led into the

cavity at the second stage. The flap is held against its bed of chest wall by packing, or by bringing the edges of the skin defect up against it. This concludes the first stage. If the cavity is opened and the flap introduced into it at a single sitting it is liable to be blown out of place by pressure of air expelled from the cavity during cough and is prone to tuberculous ulceration. Since one of us (W. L. R.) proposed this two-stage procedure, by which the flap becomes firmly attached to its aseptic new bed before the cavity is opened, these accidents have no longer frustrated the plan of operation. About two or three weeks later the cavity is opened with a large galvanocautery or with an electrical knife; a broad metal retractor or a wooden tongue-blade pushes the flap aside, protecting it from injury. Its free tip is pushed into the cavity and held in place for a week or so by vaseline gauze packing.

Axillary flaps for apical cavities are easy to fashion, both before and after thoracoplasty. More troublesome to drain are cavities in the apex of the lower lobe for which the procedure may be peculiarly suited. These cavities lie attached to the posterior pleura between the scapula and the spine. They can be reached only by a posterior route, traversing of necessity the masses of trapezius and rhomboid musculature. The pleura may lie two or more inches from the skin surface, which in itself means a long flap. A flap with a lateral base cannot be used, for the movements of the scapula pull it away from its attachment to the pleura or to the cavity. It has, therefore, to be fashioned with its base lying superiorly and medially and with its tip brought well out onto the skin that overlies the scapula. Care should be taken that these thick flaps adhere well before opening the cavity.

The after-care is equally simple. Drainage is not profuse enough to demand frequent changes of dressing. Gauze, rubber-tubes and other foreign materials should not be poked along the skin flap into the cavity; to do so frustrates its design. The flap is left in place until the cavity is closed and until both sputum and whatever minimal suppuration there may be along the sinus tract consistently fail to show tubercle bacilli. Then, after a year or more, it may be detached under local anesthesia and sewn loosely back into the place it was taken from.

While our experience with this procedure is not extensive and cannot compare with that of Monaldi, Kupka, Vacarezza, Dobric, Vineburg and others who have occupied themselves with the problem of the insufflated cavity, the method of attack described above differs in some essential details both from the long attempted open drainage and from closed drainage with a tube or cannula as used by other investigators; moreover some of our operations date far enough back to give an idea of their later course, development and outcome; we have thought, therefore, that publication of this small series may be not unwarranted.

For the most part, the patients upon whom the flap has been used were those of a small private institution, of good economic status, whose aim was early restoration to earning power or economic usefulness. Consequently, they were of a type who might be expected to coöperate fully, both in putting up with the disagreeable features of a draining sinus for a time, and in observing those rules

which provide for continued good health of the arrested case of tuberculosis after discharge. Whatever good results have been attained may be ascribed in large measure to these factors.

The first patient so treated, whose onset was in 1937, was referred by Dr. Philip H. Pierson and is listed as No. 1 in table 1. He was a white dentist, aged thirty, and had had a stormy course both before and after entering the sanatorium. A large cavity occupying most of the right upper lobe had resisted thoracoplasty, seeming to balloon out rather than to fall in after the upper seven ribs were removed in January, 1939. It seemed obvious therefore that the cavity fell into the group previously described by one of us (L.E.) as "blocked" cavities and that some check-valve mechanism was operating to "balloon out" the right upper lobe.

It was at this time that Dr. Edward Kupka, then a fellow at the Forlanini Institute near Rome, wrote us about the interesting results obtained there by Doctor Monaldi with his suction drainage experiments. Believing therefore that no amount of compression alone could possibly furnish the answer in a case such as that described above, and bearing in mind Eloesser's earlier experiences with bronchial tuberculosis, subsequent stenoses and "blocked cavities," it was decided to investigate the dynamics of the cavity in question. Accordingly, 17-gauge blunt needles were introduced into the cavity and allowed to remain in place for several hours to several days. Interestingly enough, the initial pressure in the cavity was found to be about 20 cm. of water, rising at times so high that it could not be measured on the ordinary manometer of the pneumothorax apparatus. Interesting also were two additional facts: first, that the cavity promptly disappeared radiographically with reduction of intracavitary pressure to an atmospheric level and, second, that the patient improved clinically. The needle was therefore replaced by a catheter on June 5, 1939. This was allowed to remain in place until July 24, 1939 at which time it was withdrawn. The cavity reappeared and seemed to be as large as ever.

Finally we were reluctantly forced to the conclusion that the only way to deal successfully with such a large tension cavity was to provide adequate, more or less permanent drainage. Accordingly, a U-shaped incision was made in the axilla with its base upward so that the flap of skin might protect the axillary contents. A section of the regenerated fourth rib was excised, a large cavity opened and the skin flap sutured to its upper border with two chromic gut sutures. The cavity was then packed with iodoform gauze. For the succeeding forty-eight hours the patient's temperature rose to 105° F., although he felt quite well. The iodoform gauze was removed in the belief that this had led to the extreme elevation of temperature. With this the temperature promptly fell to 100°F., the cavity rapidly became smaller and then closed, leaving a small sinus tract which also closed spontaneously. Simultaneously the sputum ceased and has never reappeared. The patient returned to his work as a dentist and when last seen in February, 1944 was still perfectly well, the roentgenogram showing only a small amount of fibrosis in the right upper lobe beneath the thoracoplasty.

The striking success of this procedure in the first case led to further trial. In the above private institution a conservative type of apical thoracoplasty had been used which consisted in the removal of the first, second and half of the third rib at the first stage, followed by a second stage with removal of the anterior half of the third and sections of the fourth and fifth ribs, but without removal of the transverse processes or the costal cartilages. The apical drop was sometimes disappointing with this type of operation, but it seemed to have the advantages that complications, such as spread of the disease, did not occur and that postoperative mortality was nil. It had the additional advantage that it could be used in very ill patients, often with bilateral disease. Two-thirds of



FIG. 1. Axillary flap healed five years after flap drainage

the patients so operated upon, were back at work within one year. Nevertheless, in 4 per cent there remained residual cavities beneath such thoracoplasties. These have been dealt with largely by the flap method if they did not close spontaneously in a few months.

#### RESULTS

Table 1 lists 24 cases. Upper lobe cavities have been opened beneath thoracoplasties. Lower lobe cavities have been opened posteriorly in conjunction with phrenic interruption. Twelve upper lobe cavities may be said to have disappeared satisfactorily. One was a complete failure. This was not an insufflated





FIG. 2. Type of cavity treated successfully by posterior skin-flap.

(Upper left) Cavity filled with lipiodol, patient supine.

(Upper right) Needle introduced into cavity which disappears with atmospheric pressure.

FIG. 3. (Bottom) Large cavity in upper part of left lower lobe with catheter inserted to show anterior limit of cavity. Phrenic interruption followed by skin-flap drainage.

TABLE 1  
*Skin-flaps in treatment of insufflated cavities*

CASE	LOCATION OF CAVITY	AGE	SEX	ONSET	PRIOR TREATMENT	DATE	TYPE AND DATE OF FLAP OPERATION	RESULT
1	R.U.	30	M	1937	Pneumo-thorax, thoracoplasty 7 rib	1938 1939	Axillary, 1939	No sputum. Working.
2	L.U.	19	F	1938	Pneumo-thorax, extrapleural thoracoplasty	1938 1938 1939	Posterior, Sept. 1940	Cavity apparently closed. Recent cavity behind heart.
3	L.U.	24	F	1938	Thoracoplasty	Aug. 1940	Posterior, Nov. 1940	No sputum. At work.
4	R.U.	40	F	1939	Thoracoplasty anterior and posterior	1939	Axillary, Oct. 1940	Cavity persists. Sputum positive.
5	R.U.	31	F	1940	Thoracoplasty	Oct. 1940	Posterior, Nov. 1941	No sputum. At work.
6	L.U.	18	F	1940	Thoracoplasty	Nov. 1940	Posterior, Jan. 1942	No sputum. House-work.
7	L.U.	27	M	1938	Thoracoplasty	Dec. 1940	Posterior, Mar. 1942	Well when last heard from.
8	R.U.	41	F	1940	Thoracoplasty	1941	Posterior, June 1942	Cavity apparently closed. Sputum positive. Source undetermined.
9	L.U.	34	F	1939	Thoracoplasty	1941	Posterior, June 1942	Well when last heard from.
10	L.L.	26	F	1936	Phrenic crush	1942	Posterior, July 1942	No sputum. At work.
11	L.U.	29	M	1940	Bed-rest	1942	Lateral, May 1942	No sputum. At work.
12	L.L.	20	M	1938	Phrenic crush	1942	Posterior, Aug. 1942	No sputum. At work.
13	R.L.	31	M	1939	Phrenic crush	1942	Posterior, Aug. 1942	No sputum. At work.
14	L.U.	36	F	1939	Thoracoplasty	July 1942	Posterior, Aug. 1942	First-stage flap done, followed by pneumoperitoneum. Cavity closed.

TABLE 1—*Concluded*

CASE	LOCATION OF CAVITY	AGE	SEX	ONSET	PRIOR TREATMENT	DATE	TYPE AND DATE OF FLAP OPERATION	RESULT
15	R.L.	12	F	1941	Phrenic neurectomy	1942	Posterior, July 1943	Cavity present. Wound closed in three weeks.
16	L.L.	40	F	1937	Phrenic crush	Dec. 1940	Posterior, May 1943	Sputum negative on concentration. Doing housework.
17	R.U.	46	M	1941	Thoracoplasty	Oct. 1942	Feb. 1944	No sputum. In sanatorium.
18	R.U.	31	M	1940	Pneumothorax, thoracoplasty	1940 1940	Posterior, May 1941	Sputum positive. Lobectomy 12/30/42. Died 1/23/43.
19	L.L.	17	F	1935	Pneumothorax, phrenic crush	1936-1938 Feb. 1940	Posterior, Aug. 1941	Rib resection only; cavity closed spontaneously.
20	L.U.	19	F	April 1938	Pneumothorax, phrenicectomy, tube drainage	1938 Apr. 1939 Nov. 1939	Axillary, Apr. 1940	Thoracoplasty Aug. 1940. Good health Apr. 1941.
21	L.L.	26	F	1938	Pneumothorax, phrenicectomy	1938-1941 July 1941	Posterior, Aug. 1941	Cavity closed. Sputum and secretion negative. June 1942.
22	R.L.	45	F	1937	Tube drainage, phrenicectomy	Oct. 1939 Dec. 1939	Axillary, Jan. 24, 1940	Cavity closed and reopened. Died; miliary dissemination 12/26/42.
23	L.U.	?	M	1939	Thoracoplasty	Mar. 1941	Type ? Apr. 29, 1941	Died, meningitis, 7/4/41.
24	L.U.	35	F	1937	Phrenicectomy, thoracoplasty	1938 1938 1940	Posterior, Mar. 11, 1941	Died, meningitis, miliary tuberculosis, 7/5/41.

cavity. Five lower lobe cavities disappeared, one after the first stage, before the cavity was opened, which is included as a matter of interest only, and one was an outright failure owing to too early closure of the flap which could not be kept open. Two others were upper lobe cavities opened after thoracoplasty. Both patients, one male and one female, developed tuberculous meningitis within six weeks of opening and died after the usual course of tuberculous meningitis. It seems reasonable to ascribe this to trauma produced when the cavities were opened. In both of these cases the openings were made with the actual cautery.

Four cases done at other hospitals are listed. As will be seen, 3 may be classed as successful, one as a failure.

In all, therefore, 24 cases are listed, 23 of which had cavity flaps completed; 18 were satisfactory in cavity closure; 3 were similarly unsatisfactory; 2 led to the development of tuberculous meningitis.

#### CRITERIA FOR THE USE OF FLAP DRAINAGE

Whether, in view of the somewhat questionable results obtained in the above brief series, one will wish to attempt cavity drainage will, of course, depend upon the viewpoint of the clinician. If the attempt is made, however, it would seem wise to observe the following facts and indications:

Tuberculous intrapulmonary cavities apparently form in two ways: first, by the excavation of a more or less solid cheesy area of lung tissue, in which case they are often irregular in outline, with pseudopodia or extensions as may be demonstrated by the injection of lipiodol; second, they may occur as the result of check-valve bronchial mechanisms, in which event they often appear as spherical areas in otherwise little affected lung. However, as encountered in practice, particularly by the time they reach the surgeon, they often maintain their patency by not only being "blown up" by the check-valve mechanism but also by adherent pleura overlying them. We have spoken of the former as the "intrinsic" or bronchial factor and the latter as the "extrinsic" or chest wall factor. In order to deal adequately with insufflated cavities, therefore, both factors should theoretically be dealt with, first the extrinsic, then the intrinsic.

Flap drainage of insufflated cavities, therefore, should be done only under the following conditions if disappointment is to be avoided:

- 1: Thoracoplasty should have been done for upper lobe cavities. (Extrinsic factor dealt with.)
- 2: Phrenic interruption should have been done for lower lobe cavities. (Extrinsic factor dealt with.)
- 3: The residual cavity should still be an insufflated one as shown by manometer readings. (Intrinsic factor still operative.)
- 4: The cavity should then be opened in such a manner that the opening will remain adequate over a long period of time.

In conclusion it should be said that the authors still consider this method of treating residual tuberculous cavities as on trial. In certain cases it has seemed to be satisfactory. It may be, however, that newer methods of treatment, such as lobectomy, will render the procedure unnecessary. It may be, too, that more extensive thoracoplasties in the hands of others render the employment of such a procedure unnecessary. At best, it is one method of dealing with a difficult situation. It may prove of especial value in dealing with cavities of the apex of the lower lobe.

#### SUMMARY

A method of treating residual tuberculous cavities beneath thoracoplasties or in conjunction with other collapse measures, such as phrenic crush, is described. It is presumed that these cavities are in reality insufflated cavities which persist

because of tension secondary to check-valve mechanisms in their draining bronchus or bronchi. Non-insufflated cavities are excluded. Twenty-four cases are listed, 23 of which had cavity flaps completed. A skin-flap was fastened to the cavity wall and the cavity then opened with cautery. Eighteen were satisfactory in regard to cavity closure. Three were unsatisfactory. Two developed tuberculous meningitis postoperatively. It is believed that, if disappointment is to be avoided, a collapse procedure such as thoracoplasty should be done before the flap is undertaken if the residual cavity should still be an insufflated one. The cavity should then be opened in such a manner that the opening will remain patent over a long period of time.

#### SUMARIO

Discútese aquí un método para tratar las cavernas tuberculosas residuales que quedan debajo de las toracoplastias, utilizando el mismo ya solo o unido a otras medidas de colapso, tales como la trituración del frénico. Supónese que esas cavernas representan en realidad cavernas infladas que persisten debido a la existencia de una tensión debida a los mecanismos de válvula en el bronquio o bronquios que las canalizan. Exclúyense otras cavernas. Enuméranse 24 casos, en 23 de los cuales se habían tallado colgajos de las cavernas y asegurado a la pared, incindiendo luego la caverna con un cauterio. Dieciocho resultaron satisfactorios en cuanto a la obturación de la caverna y tres no. En dos se presentó meningitis tuberculosa postoperatoria. Exprésase aquí la opinión de que si van a evitarse desengaños debe ejecutarse algún procedimiento de colapso tal como la toracoplastia antes de ejecutar el colgajo si la caverna residual está todavía inflada. Luego debe abrirse la caverna de modo que la abertura permanezca permeable durante un período prolongado.

#### DISCUSSION

*Dr. E. J. O'Brien, Detroit, Michigan:* Doctor Maier's paper is one of the most complete and comprehensive ones on the subject of blocked cavities that I have yet heard. I agree entirely with all he says about the mechanics involved and resultant change in physiological function. I do not agree, however, with the implied conclusion that lung resection might be the method of choice in overcoming the difficulties caused by this condition. As he says, it is difficult to be sure when the condition exists, or that it might not change either with or without collapse measures. One may find intracavitary pressure readings suggestive of blocked cavities to-day, and in a few weeks find the readings may be normal or one may even find the cavity closed, with or without collapse measures. Many cavities apparently blocked close readily after collapse. The only time we may be sure a cavity is blocked, and probably will remain so, is after the completion of collapse measures. If the cavity is still open and apparently blocked after collapse, resection of the lung may be the procedure of choice. It is not much more difficult to remove the lung, or segments of it, after thoracoplasty is completed. We have had excellent results, however, with partially stenosed bronchi following dilatation of the stricture before and between the stages of thoracoplasty. A stenosis that does not respond to dilatation can be given the help afforded by resection. Even with residual cavities following thoracoplasty, however, cavernostomy has closed the cavity in about 70 per cent of our small series of cases. The

results of collapse therapy in all forms of cavities are so good that it does not seem to me that we are justified in doing lung resection when we first suspect blocked cavities. Up to date, the results of resection, with its high fatality rate, resultant fistulae, spreads, persistent positive sputum, etc., do not justify the procedure unless all collapse measures have been tried.

The skin-flap operation suggested in the paper by Doctors Eloesser, Rogers and Shipman, I think is an excellent one and can be used very effectively when cavernostomy is indicated. I agree entirely with their statements that the extrinsic factors of the bony cage, overlying cavities is the cause of many failures from cavernostomy, and believe that these overlying ribs should be removed to allow relaxation of the cavity walls and lung parenchyma. I am not in accord with the limited thorocoplasty proposed. I do not think one can set up a limited operation that will take care of all situations. One must do enough rib resection to cause cavity closure and this can only be determined as the stages are being done.

*Dr. John V. Thompson, Indianapolis, Indiana:* The number of patients in the following series is perhaps too small and the lapse of time since operation too short for presentation. The conditions, however, for which the procedure was carried out and the present status of the patients may be of interest.

Open drainage of the cavity was carried out in 11 poor-risk patients with residual tuberculous pulmonary cavities in the following circumstances: (1) after the maximum degree of collapse possible had been achieved by various procedures; (2) when further collapse was contraindicated or inadvisable for various reasons; (3) where additional collapse would result in the loss of function of relatively good lung tissue. It appeared advisable to have other pulmonary lesions under control or good possibilities of same.

The procedure seemed to be relatively safe, well tolerated and accompanied by few complications with the described technique. The use of the Eloesser skin-flap as described by Shipman and his colleagues, together with wide lateral unroofing of the cavity are important for the continued adequate drainage of the cavity.

Drainage appears to aid in symptomatic relief, particularly of hemorrhage from the cavity and in the recovery from tuberculous bronchitis with its complications.

In regard to the present status of the patients, 4 are ambulant and the others are being kept on bed-rest as yet. The first patient operated on early in 1942 was discharged twenty months ago and is working full time.

Sputum conversion occurred in all patients. In one instance, the sputum became positive after a year, when the patient developed an exacerbation of the pulmonary lesions.

There is no bronchial fistula in 10 of the patients. A small fistula is present in one patient operated on within the last three months.

The wounds of 4 patients are completely healed. Those of 3 are nearly epithelialized and a healed wound is anticipated in the near future. The other 4 patients were operated on within the last six months and have granulating wounds which appear to be filling in with satisfactory progress.

# PULMONARY RESECTION IN THE TREATMENT OF PULMONARY TUBERCULOSIS<sup>1,2</sup>

RICHARD H. OVERHOLT AND NORMAN J. WILSON

During the past decade pulmonary resection as a form of treatment for pulmonary tuberculosis has been applied to a steadily increasing number of patients. In the earlier years of this period results were discouraging because of the relatively high operative mortality and the prohibitive incidence of serious complications, such as contralateral spread, empyema and bronchial fistula. However, progress has been rapid in the field of thoracic surgery in the past few years so that the entire picture has changed and become more hopeful. Newer and better operative techniques have been developed, especially the individual ligation of the hilar structures and the pleural flap method of reinforcing the bronchial closure. Rapid strides have also been made in the allied fields of anesthesiology and bronchoscopy. Intratracheal anesthesia administered by trained anesthetists has enabled the thoracic surgeon to perform tasks that otherwise would have been impossible. Bronchoscopy has revealed the high incidence of bronchial tuberculosis. This has permitted a more intelligent approach to pulmonary resection in these cases and has prevented many of the mistakes and failures experienced in the earlier years. A new era of chemotherapy of infection was also ushered in with the advent of the sulfonamides and, more recently, penicillin. All of these improvements have steadily reduced the mortality and complications associated with lung resection. In fact, pulmonary resection can be performed to-day with such a margin of safety that it should be considered in any therapeutic program in treating tuberculous patients.

Since 1934, 97 pulmonary resections have been performed in the treatment of tuberculosis by one of us (R. H. O.). The present report deals with the 60 operations performed between January 1, 1942, and January 1, 1944.<sup>3</sup> The 18 patients operated on prior to this time have been omitted because during the early years the operative technique and the criteria for the selection of patients were not well standardized. During that time the pleural flap method of closing the bronchus was not routinely used and in a few cases the tourniquet method of handling the hilum was employed. The patients operated on since January 1, 1944 have been omitted because the follow-up period has been too short to permit evaluation of their condition.

## GENERAL STATISTICS

Table 1 presents the general statistics. Sixty resections were performed upon 59 patients. One patient had two lobectomies. There were 36 pneumonecto-

<sup>1</sup> From the New England Deaconess Hospital, Boston, Massachusetts.

<sup>2</sup> Presented before the Medical Section at the 40th annual meeting of the National Tuberculosis Association, Chicago, Illinois, May 11, 1944.

<sup>3</sup> An inclusive report on all patients treated by resection between 1934 and July 1, 1943 has been submitted for publication (5).

mies, 14 on the right and 22 on the left; and 24 lobectomies. We should like to call special attention to the 6 left upper lobectomies. These were all performed with individual ligation technique without any unusual technical difficulties.

TABLE 1  
*General statistics*

I	Number of patients.....	59
II	Number of resections.....	60
	A. Pneumonectomies.....	36
	1. Right.....	14
	2. Left.....	22
	B. Lobectomies.....	24
	1. Right upper.....	6
	2. Right upper and middle.....	2
	3. Right lower and middle.....	1
	4. Right lower.....	5
	5. Left upper.....	6
	6. Left lower.....	4
III	Preoperative classification	
	A. Reasonable risks.....	47
	B. Desperate risks.....	13
IV	Age of patients—15 to 54 years	
	A. 15 to 20.....	1
	B. 20 to 30.....	23
	C. 30 to 40.....	26
	D. 40 to 50.....	5
	E. 50 to 55.....	4
V	Sex	
	A. Females.....	38
	B. Males.....	21
VI	Duration of illness	
	A. Under 6 months.....	6
	B. 6 months to 1 year.....	8
	C. 1 year to 2 years.....	16
	D. 2 years to 3 years.....	7
	E. 3 years to 4 years.....	7
	F. 4 years to 5 years.....	5
	G. 5 years to 10 years.....	6
	H. 10 years to 15 years.....	4
	I. 19 years.....	1
VII	Incidence of tuberculous bronchitis—31.7 per cent (19 cases)	
	A. Submucosal type.....	1
	B. Ulceration.....	5
	C. Ulcero-stenosis.....	9
	D. Fibrous stenosis.....	4
VIII	Incidence of positive sputum—90 per cent (54 cases)	



Our experience here is contrary to that of Kent and Blades (3) who stated in 1942, with reference to the left upper lobe, "Except under unusually favorable circumstances, individual ligation technique for resection will be hazardous or impossible."

The patients were classified preoperatively according to the risk involved. Thirteen were classified as desperate risks. These were patients in whom an early fatal course was anticipated. Not only in our opinion, but in the opinion of every physician concerned, pulmonary resection offered them their only chance to get well. The reader is referred to table 8 for details concerning these cases. Analysis of this table will reveal that 11 had active progressive tuberculosis, 8 had tuberculous bronchitis and 2 had contralateral lesions involving the upper third of the lung. One patient, who had previously had extensive thoracoplasty, had a vital capacity of 900 cc. before left pneumonectomy was performed. One had had pulmonary tuberculosis for nineteen years.

There were 47 patients classified preoperatively as reasonable risks. We do not wish to infer by this classification that these patients had stabilized forms of tuberculosis or that the operation was elected in preference to thoracoplasty. On the contrary, the vast majority of these patients had extensive, active, progressive tuberculous lesions. In 32 patients thoracoplasty was either considered to be contraindicated or failure was anticipated. In our opinion, thoracoplasty might have been used with some hope of success in only 15 of the cases.

The remainder of the table is self-explanatory. We should like to call attention, however, to the very high incidence of tuberculous bronchitis, which was present in 31.7 per cent; also to the high incidence of positive sputum, 90 per cent. The 6 patients who had negative sputum at the time of resection are represented by the following:

1: One patient previously had tuberculosis in the right lower lobe which was controlled by pneumothorax. The resection was performed for residual bronchiectasis involving the right lower and middle lobes.

2: One whose tuberculosis had been controlled by an extensive left thoracoplasty still was incapacitated by recurring pulmonary hemorrhages. Her vital capacity was 900 cc. at the time of operation.

3: One had pulmonary tuberculosis for ten years and a right pneumothorax for four years. A slowly progressive lesion was present in the left upper lobe which at the time of resection involved almost the entire lobe. In spite of this extensive disease, a positive sputum was never secured from the patient (except once in January, 1943). (See figure 2.)

4: One patient had an extensive involvement of the right lower lobe which had been partially controlled by pneumothorax. However, after three years of pneumothorax, the sputum was still intermittently positive and frequent hemoptyses occurred. For this reason, the small, opaque, right lower lobe was resected.

5: One had pneumothorax for several months. The sputum had been converted, but his lung had become opaque and unexpandable. Fluid formed in the pleural space which was positive for tubercle bacilli on guinea pig inoculation.

6: One patient had a tuberculoma in the right upper lobe.

## INDICATIONS

Table 2 presents the indications for the 60 resections. Associated suppurative disease was the indication in 2 cases. Both had bronchiectasis. The tuberculosis was apparently arrested in one and was active in the other.

Uncontrolled disease following thoracoplasty was the indication in 9 cases. One-third of this group had endobronchial tuberculosis. Two of these patients previously had a revisional thoracoplasty. Resection was performed in preference to a revisional thoracoplasty in 5. In the remaining 2 cases, revisional

TABLE 2  
*Indications*

I	Associated suppurative disease—2 cases	
	A. Tuberculosis controlled	1
	B. Tuberculosis uncontrolled	1
	Total	2
II	Post-thoracoplasty uncontrolled disease—9 cases	
	A. No endobronchial tuberculosis	6
	B. With endobronchial tuberculosis	3
	Total	9
III	Extensive multilobar predominantly unilateral tuberculosis—29 cases	
	A. No endobronchial tuberculosis	13
	B. With endobronchial tuberculosis	16
	Total	29
IV	Extensive upper lobe tuberculosis—8 cases	
	A. No endobronchial tuberculosis in this group	
V	Basal tuberculosis—9 cases	
	A. No endobronchial tuberculosis in this group	
VI	Recurrent hemorrhages—tuberculosis controlled with thoracoplasty—1 case	
VII	Tuberculoma—1 case	
VIII	Giant cavities in both upper lobes—1 case	

thoracoplasty was considered to be contraindicated because of a flaccid chest wall in one and because of an extensive spread to the lower lobe following the initial thoracoplasty in the other. Four of the patients in this group were treated by lobectomy and 5 by pneumonectomy.

The most common indication in this group was extensive multilobar disease which was predominantly unilateral. This was present in 29 patients, all of whom were treated by pneumonectomy. Sixteen had tuberculous bronchitis involving the major bronchi. Extensive thoracoplasty as an alternative form of treatment might have been used with doubtful results in only 7 patients of this

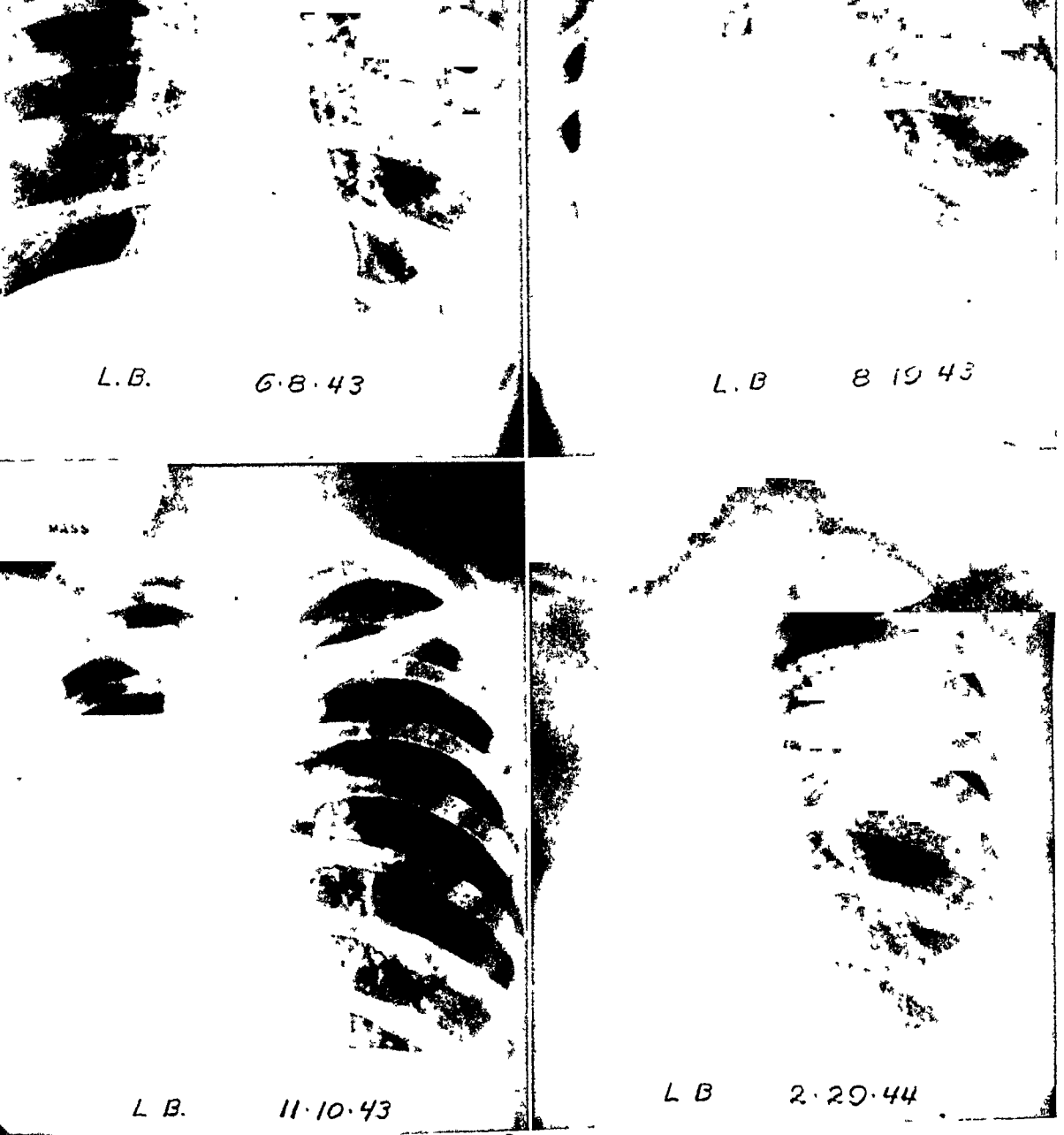


FIGURE 1A

Mrs. L. B. Age twenty-three. Case #70 in table 8. Onset of tuberculosis eight months prior to resection. Right pneumothorax instituted in July, 1943. Right lung became opaque. Bronchoscopy negative. Right pneumonectomy performed on October 11, 1943. Patient had an uneventful postoperative course. Has been asymptomatic since operation and her sputum has been consistently negative, including guinea pig inoculation.

Upper left: Roentgenogram of June 8, 1943 showing exudative lesion with small cavity at right apex and a small amount of infiltration near the hilum. Left lung clear.

Upper right: Roentgenogram of August 19, 1943, shortly after the induction of right pneumothorax. Note the dense opacity involving the major portion of the right lung and the cavity at right apex. A small nodular spread is present in left lung in middle third.

Lower left: Roentgenogram one month following right pneumonectomy.

Lower right: Roentgenogram of February 29, 1944, four and one-half months following resection.

entire group. In the remaining 22, the failure of thoracoplasty was anticipated or thoracoplasty was actually considered to be contraindicated.

Extensive tuberculosis of the upper lobe was the indication in 8 cases. There was no involvement of the major bronchi in this group. All cases were treated by lobectomy except one. In this patient a pneumonectomy was performed because of extensive involvement of the superior division of the left lower lobe.

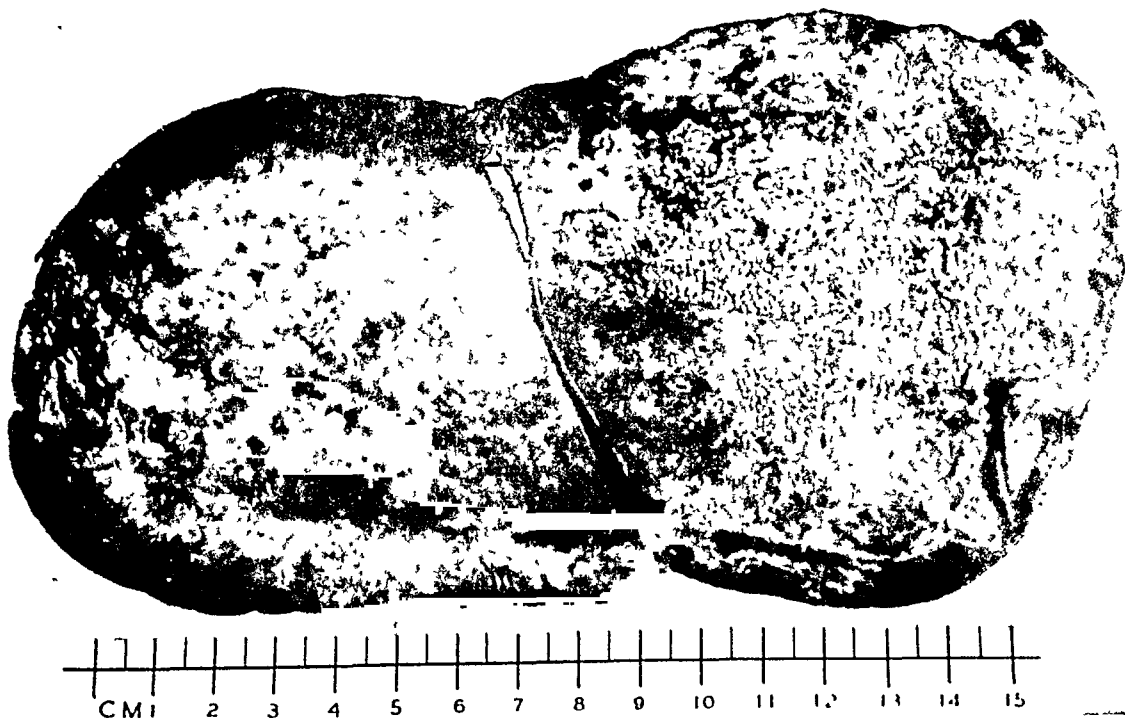


FIGURE 1B

Surgical specimen (right lung) which revealed extensive involvement of the entire lung with nodular caseous foci measuring up to 0.6 cm. These were predominantly in the upper and lower lobes. There was moderate involvement of the middle lobe. There was extensive involvement of the bronchi throughout the lung. The bronchial segment adjacent to the bronchial suture line revealed submucosal tubercles. The pleura was only slightly thickened.

Note: This specimen shows that the dense opacity which developed suddenly following pneumothorax was not atelectasis but, in reality, an involvement of almost the entire lung by tuberculous nodules.

This was first discovered at surgical exploration as it had not been revealed by X-ray study.

Basal tuberculosis was the indication for resection in 9 cases. Eight were treated by lobectomy and one by pneumonectomy. Resection was used as a primary form of therapy in 3 of these patients. Another had had a short-term pneumothorax which was ineffective, and resection was performed without fur-

ther delay. Two had failed to control their disease with phrenic paralysis. One had residual symptoms and intermittent positive sputum after three years of pneumothorax. The remaining patient had residual symptoms and positive sputum after five years of pneumothorax and several phrenic crushes.

Recurrent hemorrhages were the indication in one and tuberculoma in one. The indication in the remaining case was bilateral giant cavities in the upper lobes. A bilateral upper lobectomy has been performed on this patient, the last resection having been done in January, 1944.

It is very difficult to present the indications for resection completely for each case. Many of the patients had failed to respond to pneumothorax, phrenic paralysis, or both. In others, pneumothorax was impossible because of pleural symphysis. For more detailed information concerning these cases, the reader is referred to table 8.

#### COMPLICATIONS

In 1942, Thornton and Adams (6) collected from the literature records of 29 pneumonectomies and 46 lobectomies. In this collected series there was a very high incidence of serious complications, particularly persistent fistula, contralateral spread and empyema. Table 3 presents a comparison between this collected series of Thornton and Adams and the 60 resections presented in this paper. This table is presented to show the progress made in the last few years, and is in no way meant to be a criticism of the earlier workers and pioneers in this field. An analysis of this table shows that two of the complications, namely, persistent fistula and empyema, have been eliminated in the 24 consecutive lobectomies. Persistent fistula occurred in only one of the 36 pneumonectomies. This fistula developed nine months following resection in a patient who had been completely well and asymptomatic up until this time. She also had, as one would suspect, a tuberculous empyema. Nontuberculous empyema occurred in 2 cases, or 5.5 per cent of the pneumonectomy cases. Both of these were caused by *Staphylococcus aureus*, and there was no evidence of tuberculous infection in either of them. The reduction in the incidence of persistent fistula and empyema has been accomplished by two important technical improvements: (1) the individual ligation technique of handling the hilar structures, and (2) the pleural flap method of closing the bronchus. The high incidence of these complications in the earlier years was due not to the tuberculous infection *per se*, but to improper technique.

Contralateral spread remains the most frequent complication and the greatest threat to the patient in resection for pulmonary tuberculosis. It occurred in 11.1 per cent of the 36 pneumonectomies and in 12.5 per cent of the 24 lobectomies. As can be seen, the incidence of this complication varied little with the type of operation. In our opinion, it is more a manifestation of the type of disease the patient has, and is more apt to occur when a large amount of secretion is present. It is caused by contralateral spilling of secretions during the operative procedure. In recent months an attempt has been made to overcome this complication. An attempt is made to ligate the bronchus as a primary step in the operation whenever it is technically possible. It is also important that the anesthetist keep

the patient in an even plane of anesthesia to prevent deep gasping breaths, and to pay strict attention to the aspiration of all secretions throughout the operation.

TABLE 3  
Complications

	THORNTON AND ADAMS COLLECTED SERIES	60 RESECTIONS (OVERHOLT) JAN. 1942 TO JAN. 1944
<i>Pneumonectomy</i> . . . . .	29 Cases	36 Cases
1. Persistent fistula . . . . .	34%	2.7%
2. Contralateral spread . . . . .	24%	11.1%
3. Empyema without fistula . . . . .	17%	5.5%
		(2 cases —both nontuberculous)
<i>Lobectomy</i> . . . . .	46 Cases	24 Cases
1. Persistent fistula . . . . .	30%	0%
2. Contralateral spread . . . . .	25%	12.5%
3. Empyema without fistula . . . . .	25%	0%

TABLE 4  
Complications

I Complications related to the tuberculous infection

COMPLICATIONS	PNEUMONECTOMY (36)		LOBECTOMY (24)		TOTAL (60 CASES)	
	Cases	Per cent	Cases	Per cent	Cases	Per cent
Wound infection . . . . .	0	0	0	0	0	0
Tuberculous empyema . . . . .	1	2.7	0	0	1	1.6
Nontuberculous empyema . . . . .	2	5.5	0	0	2	3.3
Temporary fistula . . . . .	0	0	1	4.1	1	1.6
Permanent fistula . . . . .	1	2.7	0	0	1	1.6
Contralateral spread . . . . .	4	11.1	3	12.5	7	11.6
Ulceration of bronchial stump . . . . .	4	11.1	1	4.1	5	8.5
Contralateral exacerbation . . . . .	3	8.3	0	0	3	5.0
Contralateral lesion developing late . . . . .	1	2.7	0	0	1	1.6
Contralateral pleurisy with effusion . . . . .	1	2.7	0	0	1	1.6
Tuberculosis of chest wall . . . . .	3	8.3	0	0	3	5.0
Ipsilateral spread . . . . .	—	—	2	8.2	—	—
Ipsilateral exacerbation . . . . .	—	—	2	8.2	—	—

II Complications related to surgical problem of pulmonary resection:

A. Paroxysmal irregular heart action with sudden death . . . . .	1
B. Circulatory collapse . . . . .	1
C. Embolism . . . . .	1
D. Postoperative shock . . . . .	1
E. Pulmonary insufficiency . . . . .	1

Table 4 presents a summary of all complications. There were no wound infections. A temporary fistula occurred in one patient following lobectomy. This was closed with a muscle transplant. A limited thoracoplasty was then performed. The patient did not develop an empyema. To-day he is clinically well and has a consistently negative sputum. (See figure 2.)

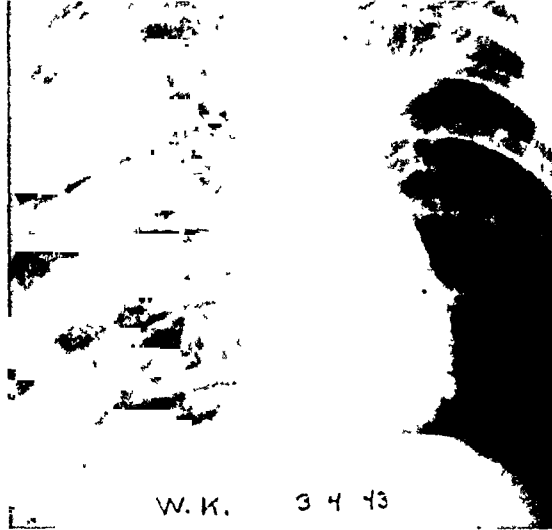


FIGURE 2A

Ulceration of the bronchial stump occurred in 4 patients following pneumonectomy, and in one following lobectomy, a total incidence of 8.5 per cent. This complication occurs much more frequently than one would suspect from the reports in the literature. It can be diagnosed only by routine bronchoscopic examination following operation. It may occur early or late in the postoperative period. We have discovered one case ten months following resection. For



FIGURE 2B

Surgical specimen (left upper lobe) showing extensive involvement with caseous nodules of the entire lobe except for the lingular segment. No cavities found. The smaller bronchi were involved.

FIGURE 2A

Mr. W. K. Age twenty-two. Case #51 in table 8. Patient had been under treatment for tuberculosis for ten years. Right pneumothorax had been present for four years and had controlled the lesion in the right lung. The lesion in the left upper lobe had slowly progressed for two years. A positive sputum was found in January, 1943. At no other time was a positive sputum secured. Left upper lobectomy was performed on March 22, 1943. The patient developed a small fistula postoperatively. On May 11, 1943, a left thoracoplasty was performed. At the same time the pleural space was opened and a muscle transplant was sutured over the fistula. An empyema did not develop. The pleural space became obliterated. The patient is asymptomatic and well. His sputum is consistently negative on concentration. Gastric specimen is also negative.

Upper: Roentgenogram of March 4, 1943, showing right pneumothorax and infiltration in left upper lobe.

Centre: Roentgenogram of May 3, 1943, six weeks following resection. Note the air and small fluid level in left pleural space.

Lower: Roentgenogram of March 20, 1944. The right lung has been reexpanded. The left lung has also reexpanded. Left lower lobe appears normal.



this reason we now advocate a routine bronchoscopic examination six weeks following resection and a repetition of this in six months if the first examination is negative. Persistence or recurrence of positive sputum may indicate stump involvement and calls for bronchoscopy. Stump ulceration must be considered as a possible source of infection in late spreads. Stump ulcers have been treated with 30 per cent silver nitrate every two weeks with gratifying results. Three of them have cleared so that at the present time there is no evidence of activity in the bronchial stump. Two of these patients are negative on guinea pig inoculation and the other is positive by guinea pig inoculation. A fourth case has been treated irregularly. She still has active ulceration in the bronchial stump and her sputum is positive. The ulcer which occurred in the lobectomy patient progressed; further resection was performed and pneumonectomy was completed. At the present time she is clinically well, although her sputum is positive on guinea pig inoculation.

Contralateral exacerbation occurred in 4 pneumonectomy patients and in none of the lobectomy cases. Two of these occurred in the postoperative period. One patient died as a result of this exacerbation and the other patient now has a stabilized lesion. At the present time he is clinically well, and is ready for discharge from the sanatorium. The third patient developed contralateral exacerbation eight months following pneumonectomy. A fourth developed a contralateral lesion eighteen months following operation. An evanescent lesion had been present in this location three months before, but this had entirely cleared before the pneumonectomy had been performed. This lesion progressed rapidly and caused the death of the patient. We believe that these contralateral exacerbations have been related not to the type of operation performed but entirely to the type and extent of preëxisting disease.

One patient developed a contralateral pleurisy with effusion three months following pneumonectomy. The pleural fluid was negative by guinea pig inoculation. This patient is at home, is well, and has a negative sputum on all tests except for guinea pig inoculation of the gastric specimen. A parenchymal lesion has never developed in the underlying lung.

In 3 patients concealed tuberculosis of the chest wall was found. These were very interesting and instructive cases. Following pneumonectomy the wound healed by primary intention in all 3, and at no time was there any indication of the underlying involvement. These patients returned for thoracoplasty and, after the incision had been made, granulation tissue was found in the soft tissues of the chest wall. Biopsy of this material revealed tissue changes consistent with tuberculosis. In spite of this, the operation was continued and thoracoplasty completed. The wound again healed by primary intention and remained healed in all 3 cases. They are all clinically well and have negative sputa at the present time.

Ipsilateral spread occurred in one patient in the postoperative period and in another case, eight months after resection. In the second instance the spread was a direct result of ulceration in the stump of the bronchus. Both cases had

extensive involvement of the bronchi on pathological examination. Ipsilateral exacerbation occurred in 2 lobectomy patients. In one, a cavity developed in the superior division of the lower lobe a few weeks following resection of the upper lobe. In the other, a fine nodular infiltration was found in the middle lobe. At the time of exploration the extent and character of the lesion hardly seemed to justify a sacrifice of this lobe. However, the lesion progressed a few months after resection.

Section 2 of table 4 deals with the complications related to the surgical problems of pulmonary resection rather than those associated with the tuberculous disease. These complications contributed to the death of the patient in each instance. This part of the table is self-explanatory.

TABLE 5  
*Fatality statistics*

<b>I Operative fatality—60 resections</b>		
Total.....		11.6% (7 of 60)
A. Reasonable risks.....	4.3% (2 of 47)	
B. Desperate risks.....	38.5% (5 of 13)	
<b>II Case fatality—59 patients</b>		
Total.....		13.6% (8 of 59)
A. Reasonable risks.....	6.5% (3 of 46)	
B. Desperate risks.....	38.5% (5 of 13)	

Note: One late death in this group of cases.

#### FATALITY STATISTICS

Table 5 presents fatality statistics. The cases have been divided, as previously described, into reasonable and desperate risks. The total operative fatality was 11.6 per cent, there being 7 deaths following 60 operations. The operative fatality for the reasonable risk cases was 4.3 per cent, representing 2 of the 47; that for the desperate risk was 38.5 per cent, representing 5 of the 13. The case fatality statistics vary little with the operative fatality because of the fact that there was only one late death in this entire group.

Table 6 analyzes the postoperative deaths. Five of the 7 patients who died in the postoperative period had been classified preoperatively as desperate risks. Five had a complicating tuberculous bronchitis. The analysis of the cause of death in these cases is quite interesting. Only 2 of the patients died of complications related to the tuberculosis. One of the reasonable risk cases died of a contralateral tuberculous pneumonia, and one of the desperate risk cases died of contralateral exacerbation associated with pulmonary insufficiency. The remaining 5 patients died of complications related to the surgical problem of pulmonary resection. Four of these were in very poor general condition prior to the operation.

As stated before, there was only one late death in this group. This occurred

in a fifteen-year-old female who developed an acute, rapidly spreading tuberculous lesion in the contralateral lung eighteen months following resection.

The analysis of these fatality statistics permit the following conclusions:

- 1: The operative fatality in reasonable risk cases is 4.3 per cent.
- 2: The operative fatality in desperate risk cases is quite high, being 38.5 per cent in this series.
- 3: Seventy-one per cent of the postoperative deaths have occurred in those classified preoperatively as desperate risks.

TABLE 6  
*Analysis of postoperative deaths*

	NAME	AGE	OPERATION	PREOPERATIVE CLASSIFICATION		DURATION OF ILLNESS	TUBERCULOUS BRONCHITIS	POST-OPERATIVE DAY OF DEATH	CAUSE OF DEATH
				Desperate risk	Reasonable risk				
1	Miss T. B.	24	Lt. upper lobectomy		Yes	22 months	0	5	Contralateral tuberculous pneumonia
2	Miss S. A.	25	Lt. pnec-tomy	Yes		5 months	0	1	Paroxysmal irregular heart action with sudden death
3	Mrs. M. M.	32	Rt. pnec-tomy	Yes		2½ years	Yes	2	Circulatory collapse
4	Mr. J. C.	54	Lt. pnec-tomy	Yes		4 years	Yes	53	Contralateral exacerbation, pulmonary insufficiency
5	Mrs. A. B.	39	Rt. pnec-tomy		Yes	11 years	Yes	15	Embolism
6	Miss M. F.	30	Rt. pnec-tomy	Yes		3 years	Yes	2 hours after op.	Postoperative shock
7	Mr. J. G.	49	Rt. pnec-tomy	Yes		19 years	Yes	19	Pulmonary insufficiency

4: Only 2, or 28.5 per cent of the postoperative deaths, have been due to the tuberculosis *per se*. The remainder of the postoperative deaths have occurred as a result of complications incident to the surgical procedure. These have occurred, with the exception of one case, in patients in very poor general condition.

5: The incidence of late deaths has been very low to date; there being but one death among the group of 52 patients who survived the two-month postoperative period.

#### COMPARATIVE RESULTS OF REASONABLE RISK CASES TREATED BY LOBECTOMY AND PNEUMONECTOMY

Table 7 analyzes the results in the reasonable risk cases. There were 25 patients treated by pneumonectomy and 22 by lobectomy. Part one of table 7

gives the most common complications encountered in these two groups. In the 22 cases treated by lobectomy, there were no permanent fistulae, no tuberculous empyemata and no nontuberculous empyemata. In the 25 patients treated by pneumonectomy, one developed a permanent fistula and tuberculous empyema. Two others had postoperative empyemata caused by *Staphylococcus aureus* which were controlled by thoracoplasty. Several factors may account for the absence

TABLE 7  
*Comparative results in reasonable risk cases—lobectomy and pneumonectomy*

		PNEUMONECTOMY— 25 CASES		LOBECTOMY— 22 CASES		TOTAL—47 CASES	
		Cases	Per cent	Cases	Per cent	Cases	Per cent
(A)	Complications						
	Permanent fistula	1	4	0	0	1	2.1
	Tuberculous empyema	1	4	0	0	1	2.1
	Nontuberculous empyema	2	8	0	0	2	4.2
	Contralateral spread	3	12	2	9.1	5	10.6
	Bronchial stump ulceration	2	8	1	4.5	3	6.3
(B)	Fatality						
	Operative fatality	1	4	1	4.5	2	4.2
	Total case fatality	2	8	1	4.5	3	6.3
(C)	Present Clinical Status						
	Clinically well with negative sputum	18	72	13	59.1	31	65.9
	Clinically well with positive sputum	2	8	2	9.1	4	8.5
	Residual symptoms (positive sputum)	2	8	—	—	2	4.2
	Fistula and empyema	1	4	0	0	1	2.1
	Dead	2	8	1	4.5	3	6.3
	Tuberculous involvement of remaining ipsilateral lobes	—	—	6	27.3	—	—
		(23 LIVING PATIENTS)		(21 LIVING PATIENTS)		(44 LIVING PATIENTS)	
(D)	Prognosis						
	Good	18	78.2	13	61.9	31	70.5
	Guarded	3	13	7	33.3	10	22.7
	Poor	2	8.7	1	4.8	3	6.8

of these complications following lobectomy. In the first place, the rapid reëxpansion of the lung after operation completely obliterates the pleural space and helps prevent the development of empyema. It also serves as an additional support to the area of the bronchial closure. The calibre of the sutured bronchi is much smaller and they are so located that less strain is exerted upon them when the patient coughs than in the case of a main bronchus.

Contralateral spread has occurred in 12 per cent of the pneumonectomy patients and in 9.1 per cent of those treated by lobectomy. This does not seem to be a significant difference.

Ulceration of the bronchial stump has occurred in 2 reasonable risk patients treated by pneumonectomy and in one of those treated by lobectomy. It is surprising that this complication should be so low in the patients treated by pneumonectomy, since 12, or 43 per cent, of this group had endobronchial tuberculosis visible through the bronchoscope. Both patients who developed this complication had an active endobronchial lesion in the orifice of the right upper lobe. Naturally, the bronchial closure was in the immediate vicinity of this involvement. The one patient treated by lobectomy who developed this complication was treated by right lower lobectomy. A study of the pathological specimen revealed extensive caseous involvement of the entire superior division bronchus. Undoubtedly that was the cause of this complication which might have been averted had a right middle and lower lobectomy been performed.

Section 2 of table 7 presents the fatality statistics. The operative fatality in both groups is almost identical, being 4 per cent in those treated with pneumonectomy and 4.5 per cent in those treated by lobectomy. There has been only one late death in either group, and this occurred in a patient treated by pneumonectomy. The total case fatality to date for the 25 patients treated by pneumonectomy is 8 per cent and for the 22 treated by lobectomy is 4.5 per cent.

Section 3 of table 7 presents the clinical status of both groups of patients. An analysis of this portion of the table will show that statistics for those treated by pneumonectomy are more favorable than for those treated by lobectomy: 72 per cent of the patients treated by pneumonectomy are clinically well and have a negative sputum,<sup>4</sup> whereas only 59.1 per cent of the lobectomy group fall into this classification. The remainder of this portion of the table is self-explanatory, except for the 6 lobectomy patients classified as having tuberculous involvement of the remaining ipsilateral lobes. Two of these patients have had spreads of residual disease. Three have residual open foci which were left behind at the time of operation. A bronchial stump ulcer was the source of spread in another. In our opinion, all 6 of these patients are failures because of the resection of too little lung tissue.

Section 4 of table 7 presents the prognosis of the 44 living patients. The prognosis is apparently good in 78.2 per cent of those treated by pneumonectomy and in 61.9 per cent of those treated by lobectomy. Of the 7 lobectomy patients with a guarded prognosis, it may be possible to change the status of 5 by further resection so that their prognosis may eventually be good. All patients classified as having poor prognosis will die of tuberculosis.

The lobectomy failures have been due to three factors which must always be considered:

- 1: Residual active foci remaining in the other lobes.
- 2: Spread of residual small foci which were considered inactive at time of resection.
- 3: Ulceration of the bronchial stump.

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<sup>4</sup> Results of cultures and guinea pig inoculations not included.

Our experience to date would indicate that it is dangerous to leave any significant amount of palpable or visible disease in the remaining lobes. These residual foci undergo some trauma during the operation and there is always some strain placed upon them during the reëxpansion of the lung.

The presence of tuberculous bronchitis is a definite hazard. Gross evidence of infection of a lobar bronchus should contraindicate lobectomy.

The statistics contained in this table are the most significant of any presented in this paper. They represent what pulmonary resection performed with modern technique offers the tuberculous patient who is in good general condition.

#### SPUTUM CONVERSION

The follow-up of this group of patients has been very difficult because the patients originated from so many different institutions and private physicians. In addition, the marked shortage of laboratory personnel has made a rigid study of the sputum impossible in a few instances. Of the 51 living patients, 14 are known to be positive on smear or concentration. With reference to the remaining 37 patients the following tabulation presents the results we now have concerning their sputum:

- 1: Twelve patients are negative on guinea pig inoculation of the sputum or gastric specimen.
- 2: In 3 patients the sputum is negative by culture.
- 3: The bronchoscopically aspirated specimen is negative in 5.
- 4: The gastric specimen is negative in 4.
- 5: Five patients are negative on concentration. Two of these are positive on guinea pig inoculation of the gastric specimen.
- 6: Six patients have been consistently negative on direct smear. All these patients are asymptomatic and clinically well. One of this group is positive by guinea pig inoculation of the gastric specimen.
- 7: Two patients have had no sputum examination since the time of resection. The reason for this is listed as "No cough or expectoration."

#### DESPERATE RISKS

Some may question the justification of separating statistics into desperate and reasonable risk groups. In fact, the advisability of accepting such desperate risk patients for resection may be questioned. However, we should like to distinguish between these patients and the poor risks described in various reports in thoracoplasty series. Those whom we have classified as desperate risks were otherwise utterly hopeless cases. In the opinion of every clinician taking care of them, resection offered them their only chance to get well. Thoracoplasty had already failed in 4, and in the remainder was considered to offer no chance of success in view of one or a combination of the following factors: bronchial involvement, giant cavitation, rapidly spreading and extensive parenchymal disease, prolonged and sustained toxemia and pyrexia, progressive weight loss or general debility. These patients meet the description of the desperate risk cases pictured by Alexander in his book *The Collapse Therapy of Pulmonary Tuberculosis*, for whom he advises against thoracoplasty. Any salvage in this group can be considered pure gain.

TABLE 8

## Résumé of 60 consecutive pulmonary resections

NAME	AGE	SEX	CASE NUMBER	PREOPERATIVE CLASSIFICATION	DATE OF OPERATION	INDICATION	ENDOBRONCHIAL TUBERCULOSIS	SPUTUM	DURATION OF DISEASE	PREVIOUS THERAPY		OPERATION PERFORMED	COMPLICATIONS		POSTOPERATIVE HOSPITAL DAYS	SPUTUM AT PRESENT	PRESENT CLINICAL STATUS
										Contralateral lung	Ipsilateral lung		Postoperative	Late			
19 M. R.	40	F	1785	R. R.	1/6/42	I A	?	0	10 years	0	Pntr., empyema Schede	Rt. M. & L.	0	0	30	Neg.	Well
20 E. M.	36	F	1907	R. R.	1/28/42	I B	?	+	7 months	0	0	L. L. L.	0	0	—	Neg.	Well
21 A. R.	32	F	1575	R. R.	2/19/42	III B	+	+	6 years	0	Pntr.	Left pnce-tomy	0	0	27	Neg.	Well
22 E. A.	34	F	1172	R. R.	4/9/42	III B	+	+	2 years	0	Phrenic	Rt. pnce-tomy	0	Stump ulceration	20	Neg.	Well
23 R. B.	52	F	226	D. R.	4/27/42	VI	0	0	4½ years	0	Thpl., phrenic	Left pnce-tomy	0	0	23	Neg.	Well
24 M. S.	26	F	1634	R. R.	5/14/42	V	0	+	2 months	0	Phrenic	L. L. L.	0	0	18	Neg.	Well
25 D. B.	26	F	1900	R. R.	5/15/42	V	0	+	3 months	0	Pntr.	R. L. L.	0	Stump ulceration, spread to rt. upper	14	+	Had R. U. & M. lobectomy in Jan. 1944
26 J. G.	28	F	1187	R. R.	6/18/42	V	0	+	2½ years	0	0	R. L. L.	Spread to rt. M. & U. lobes	0	21	+	Had rt. U. & M. lobectomy on 4/13/43
27 M. B.	28	F	1755	R. R.	6/29/42	IV	0	+	2½ years	0	Phrenic, pntr.	L. U. L.	0	0	20	Neg.	Well
28 S. B.	15	F	1966	R. R.	7/17/42	III A	0	+	10 months	0	Pntr.	Rt. pnce-tomy	0	Contralateral lesion 18 mos. later	18	—	Died Dec. 1943 of contralateral disease
29 P. H.	29	F	2094	R. R.	8/12/42	III B	+	+	8 months	0	0	Left pnce-tomy	0	Contralateral pleurisy with effusion	25	Neg.	Well
30 M. G.	29	F	1894	R. R.	8/25/42	V	0	+	17 months	0	Phrenic	R. L. L.	0	0	18	+	Clinically well. Sputum +
31 J. Y.	39	F	2154	R. R.	9/18/42	III B	+	+	3 years	0	Pntr.	Left pnce-tomy	0	Contralateral lesion appeared May 1943	23	Neg.	Well
32 E. B.	35	F	2200	R. R.	10/9/42	I C	0	+	3 months	0	0	R. L. L.	0	0	27	+	Has residual disease in rt. U. & M. lobes. Has had thoracoplasty

33	M. S.	41	F	2104	R. R.	10/12/42	VII	0	0	0	R. U. L. L. L. L.	0	0	—	Neg.	Well
34	E. C.	25	F	2226	R. R.	10/23/42	V	0	0	0		Contralateral spread	0	25	Neg.	Well
35	A. S.	30	F	889	D. R.	10/27/42	III A	0	0	0	Pathx., pnlysis	Emphyema (Staph. aureus)	0	26	Neg.	Well. Emphyema on- tirely closed with thoracoplasty
36	M. C.	34	F	1999	R. R.	10/29/42	II A	0	0	0	Pathx., thpl.	0	0	23	+	Has residual cavity in superior division of lower lobe
37	E. A.	33	F	1551	R. R.	10/30/42	III A	0	0	0	0	0	0	19	Neg.	Well
38	C. B.	22	M	1878	D. R.	12/ 1/42	III A	0	0	0	Phrenic, pnthx.	0	0	22	Neg.	Well
39	J. T.	34	M	2269	R. R.	12/11/42	III B	+	+	0	0	0	0	21	Neg.	Well
40	T. B.	24	F	1903	R. R.	12/31/42	II A	0	0	0	Pathx., thpl.	Contralateral spread	Stump ulcer- ation	—	—	Died on 5th p.o. day of contralateral pneumo- nia (? tuberculosis)
41	E. H.	38	M	2309	R. R.	1/12/43	III A	0	0	0	Pathx.	Contralateral spread, tu- berculosis of chest wall	0	22	Neg.	Well. Spread entirely healed. Incision healed by primary in- tention
42	E. C.	53	M	2260	R. R.	1/14/43	III A	0	0	0	0	0	0	21	Neg.	Well
43	M. P.	20	F	1655	R. R.	2/12/43	IV	0	0	0	Phrenic	0	0	17	Neg.	Well
44	E. P.	30	F	830	R. R.	2/18/43	II A	0	0	0	Phrenic, thpl., revision	0	0	18	+	Clinically well. Slight cough and expectora- tion
45	P. G.	34	F	2364	R. R.	2/26/43	III A	0	0	0	0	0	0	14	Neg.	Well
46	I. M.	24	F	2421	R. R.	3/20/43	III A	0	0	0	Pathx.	Tuberculosis of chest wall	0	23	Neg.	Well
47	J. C.	54	M	2385	D. R.	3/29/43	III B	+	+	0	0	Exacerbation of contralat- eral disease	—	32	—	Died on 53rd p.o. day of tuberculosis and pulmonary insuffi- ciency
48	S. A.	25	F	2422	D. R.	4/ 2/43	III A	0	0	0	0	Paroxysmal ir- regular heart action	—	—	—	Died on 1st p.o. day
49	J. G.	31	F	1187	D. R.	4/15/43	III A	0	0	0	R. L. L., phrenic	Contralateral spread	0	24	+	Has progressive tuber- culosis
50	E. M.	44	F	2010	D. R.	4/16/43	II B	+	+	0	Phrenic, thpl.	0	Stump ulcer- ation	37	+	Clinically well. Slight cough and expectora- tion



TABLE 8—Continued

NAME	AGE	SEX	CASE NUMBER	PREOPERATIVE CLASSIFICATION	DATE OF OPERATION	INDICATION	ENDOBRONCHIAL TUBERCULOSIS	SPUTUM	DURATION OF DISEASE	PREVIOUS THERAPY		OPERATION PERFORMED	COMPLICATIONS		POSTOPERATIVE HOSPITAL DAYS	SPUTUM AT PRESENT	PRESENT CLINICAL STATUS
										Contra-lateral lung	Ipsilateral lung		Postoperative	Late			
51 W. K.	22	M	2374	R. R.	3/22/43	IV	0	0	10 years	Pnths.	0	L. U. L.	Temporary fistula closed with muscle transpl.	0	21	Neg.	Well
52 M. A.	34	F	1439	R. R.	4/28/43	V	0	0	3 years	0	Phrenic, pnths.	R. L. L.	0	0	17	Neg.	Well
53 I. H.	22	F	1982	R. R.	4/27/43	II A	0	+	5½ years	0	Thpl.	L. U. L.	0	0	16	+	Clinically well
54 M. M.	32	F	2402	D. R.	5/ 3/43	III B	+	+	2½ years	Phrenic	Pnths.	Rt. pnctomy	Circulatory collapse	0	—	—	Died on 2nd p.o. day
55 C. P.	25	F	1470	R. R.	5/ 7/43	IV	0	+	5½ years	0	Pnths.	R. U. L.	0	0	10	Neg.	Well
56 M. D.	33	F	914	R. R.	5/20/43	V	0	+	6 years	0	Phrenic	L. L. L.	0	0	12	+	Clinically well
57 M. C.	25	M	2052	R. R.	6/ 4/43	II A	0	+	2 years	0	Pnths., thpl., revision	Left pnctomy	0	0	19	Neg.	Well
58 A. C.	21	F	2502	R. R.	6/ 1/43	III B	+	+	7 months	0	Pnths.	Left pnctomy	0	Developed fistula and mixed empyema, Feb. 1944	20	+	Has fistula and mixed tuberculous empyema
59 M. K.	28	F	2513	R. R.	6/ 7/43	IV	0	+	2½ years	0	0	Left pnctomy	Tuberculosis of chest wall	0	16	Neg.	Well
60 L. W.	25	F	2565	D. R.	6/12/43	III B	+	+	6 months	0	0	Rt. pnctomy	Stump ulceration, contralateral spread	0	10	Neg.	Well. Stump healed with AgNO <sub>3</sub> treatment
61 G. T.	35	F	2032	R. R.	6/21/43	III B	+	+	3½ years	0	Pnths.	Left pnctomy	Empyema (Staph. aureus)	0	16	Neg.	Well
62 M. S.	34	F	2480	R. R.	6/15/43	II A	0	+	9 years	0	Phrenic, thpl.	L. U. L.	0	0	0	Neg.	Well
63 A. B.	39	F	2568	R. R.	7/ 1/43	III B	+	+	11 years	0	Pnths.	Rt. pnctomy	Embolism	—	—	—	Sudden death on 15th p.o. day

64	G. D.	53	M	2210	R. R.	8/26/43	III B	+	+	23 months	0	Phrenic	Rt. pneumectomy	? contralateral exacerbation	0	0	22	+	Clinically well
65	M. P.	38	F	2647	D. R.	9/ 2/43	III B	+	+	16 months	0	Pnths	Left pneumectomy	0	0	8	Neg.	Well	
66	L. B.	27	F	2232	R. R.	9/20/43	III A	0	+	15 months	0	Pnths	Rt. pneumectomy	0	0	10	Neg.	Well	
67	P. P.	32	F	2642	R. R.	9/21/43	III B	+	+	5 years	0	Pnths.	Left pneumectomy	Contralateral spread	0	0	17	+	Slight cough and expectoration
68	R. B.	37	M	2702	R. R.	10/ 1/43	IV	0	+	16 months	0	Pnths	R. U. L.	0	0	14	Neg	Well	
69	D. N.	31	F	2701	R. R.	10/ 7/43	V	0	+	14 months	0	0	Left pneumectomy	0	0	11	Neg	Well	
70	L. B.	23	F	2718	R. R.	10/11/43	III A	0	+	8 months	0	Pnths	Rt. pneumectomy	0	0	12	Neg	Well	
71	M. F.	49	F	2716	R. R.	10/21/43	IV	0	+	15 years	0	0	R. U. L.	0	0	11	+	Well	
72	M. F.	30	F	1731	D. R.	10/23/43	III B	+	+	3 years	0	Pnths, thpl	Rt. pneumectomy	Postoperative shock	—	—	—	Died few hours after operation	
73	J. G.	49	M	1757	D. R.	10/25/43	II B	+	+	19 years	0	Thpl	Rt. pneumectomy	Pulmonary insufficiency	—	—	—	Died on 19th p. o. day	
74	L. J.	22	F	2736	R. R.	10/29/43	IV	0	+	11 months	0	Phrenic	R. U. L.	0	Progressive disease in rt. M & L lobes	15	?	Clinically well X-ray shows spreading lesion	
75	E. C.	23	F	2726	R. R.	11/ 3/43	III B	+	+	13 months	0	Pnths	Left pneumectomy	Contralateral spread	0	0	20	+	Progressive tuberculosis
76	J. C.	35	M	2026	R. R.	11/16/43	III A	0	0	20 months	0	Pnths	Rt. pneumectomy	0	0	18	Neg.	Still forming some fluid in rt. pleural space.	
77	M. L.	24	F	2488	D. R.	12/10/43		0	+	20 months	Pnths	Pnths	R. U. L.	Cavity in apex of L. L.	0	0	10	+	Clinically well Had L. U. lobectomy 2 months later
78	A. A.	35	F	2399	R. R.	12/27/43	III B	+	+	18 months	0	Phrenic, pnths.	Left pneumectomy	0	0	10	Neg	Well	

Of the 13 desperate risks, 5, or 45.4 per cent, are clinically well and have negative sputa. Of these 5, 3 have been discharged from the sanatorium and are now leading normal, active lives. One is at home on bed-rest. The other is still in the sanatorium and is now on graded activity. The fact that 45 per cent of these patients have been salvaged seems to justify the acceptance of at least some of these desperate risks for resection.

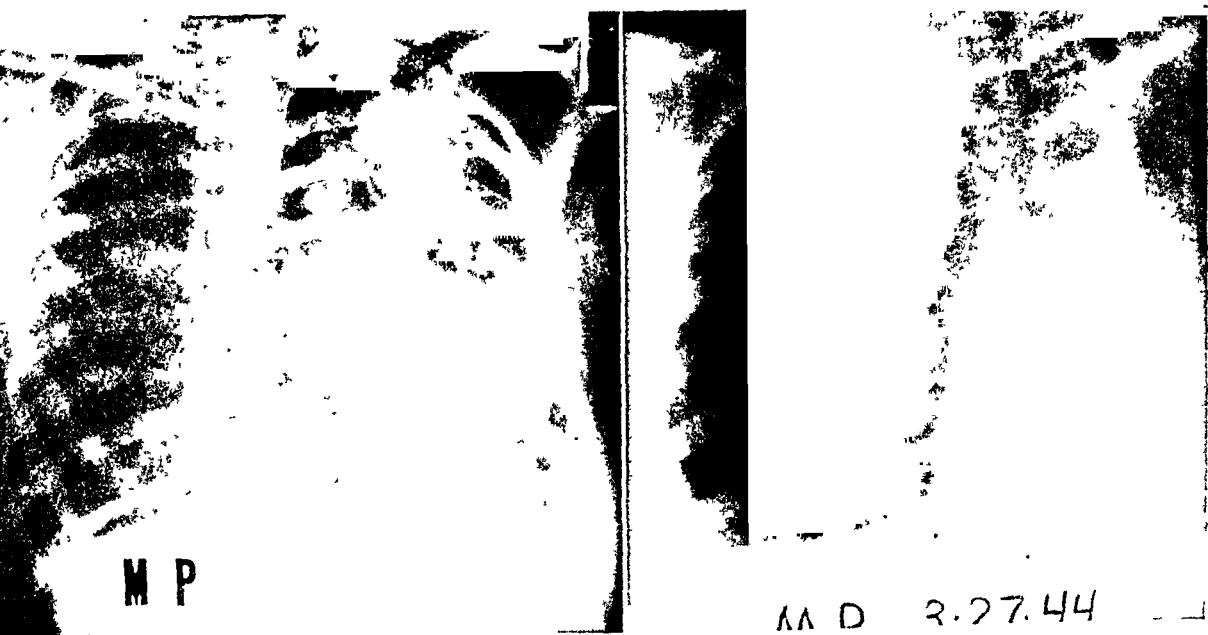


FIGURE 3A

Mrs. M. P. Age thirty-eight. Case #65 in table 8. Patient had been ill for sixteen months, during which time she had become progressively worse. Bronchoscopy revealed an ulcero-stenosis involving the left upper and lower lobe bronchi and the adjacent portion of the main bronchus. Patient was toxemic and had low grade fever. An unstable lesion was present in the contralateral lung. She was classified preoperatively as a desperate risk. Left pneumonectomy was performed on September 2, 1943. Since then the patient has been asymptomatic. Her sputum is consistently negative on seventy-two hour concentrates.

Left: Roentgenogram just prior to resection showing a huge cavity in the left upper lobe and extensive involvement of the entire left lung. Note the nodular infiltration in the right lung in the second and third interspaces.

Right: Roentgenogram on May 3, 1944 showing post-pneumonectomy and post-thoracoplasty state. A lateral type of thoracoplasty was performed six weeks after pneumonectomy to prevent mediastinal distortion and emphysema of remaining lung. This was accomplished in one stage and without removing the first rib or transverse processes. Note absence of scoliosis.

Five of these patients have died during the postoperative period. The remaining 3 will eventually die of tuberculosis.

The justification for the separation of statistics lies in the fact that none of the desperate risks would have been accepted for thoracoplasty in the vast majority of thoracic clinics. Thus, the statistics of the reasonable risks offer a series of cases in which the results may be compared with those of the various collapse therapy reports.

## THE PROBLEM OF THE CONTRALATERAL LUNG

The evaluation of the condition of the contralateral lung is a matter of great importance when pulmonary resection is contemplated in the tuberculous patient. Naturally, the criteria in respect to a contralateral lesion must be more rigid when pneumonectomy is anticipated than when lobectomy is to be performed.



FIGURE 3B

Surgical specimen (left lung) demonstrates the huge cavity in the left upper lobe and the extensive involvement of the entire lung by caseous foci. The bronchi were extensively involved. The following is the pathological report: "Cut surface shows a diffuse scattering of yellow-gray nodules throughout both lobes, but especially in the lower lobe about equal in dorsal and inferior portions. The majority of the upper lobe, except anterior portion, is occupied by an irregular cavity 8 x 4 x 4 cm. which is in direct communication with a main branch of the upper lobe bronchus near its origin. All bronchi show granular mucosa and thickened walls. The main stem bronchus shows marked narrowing of its lumen down to about 0.3 x 0.5 cm. Hilar nodes are enlarged and contain many gray nodules."

Following pneumonectomy, bed-rest alone must be relied upon to control the remaining lesion. In reference to lobectomy, contralateral pneumothorax or temporary phrenic paralysis may be employed either before or after the resection. When pneumonectomy is to be performed, the contralateral lung must not harbor an uncontrolled lesion or one that is deemed uncontrollable. However, we do not agree with those who maintain that the contralateral lung must be absolutely free of involvement. Of the 59 patients in this report, 22 had

contralateral lesions. The extent of the contralateral lesion was considered to be minimal in 16. Two of these patients previously had had extensive involvement of the contralateral lung, which had cleared quite markedly and left behind

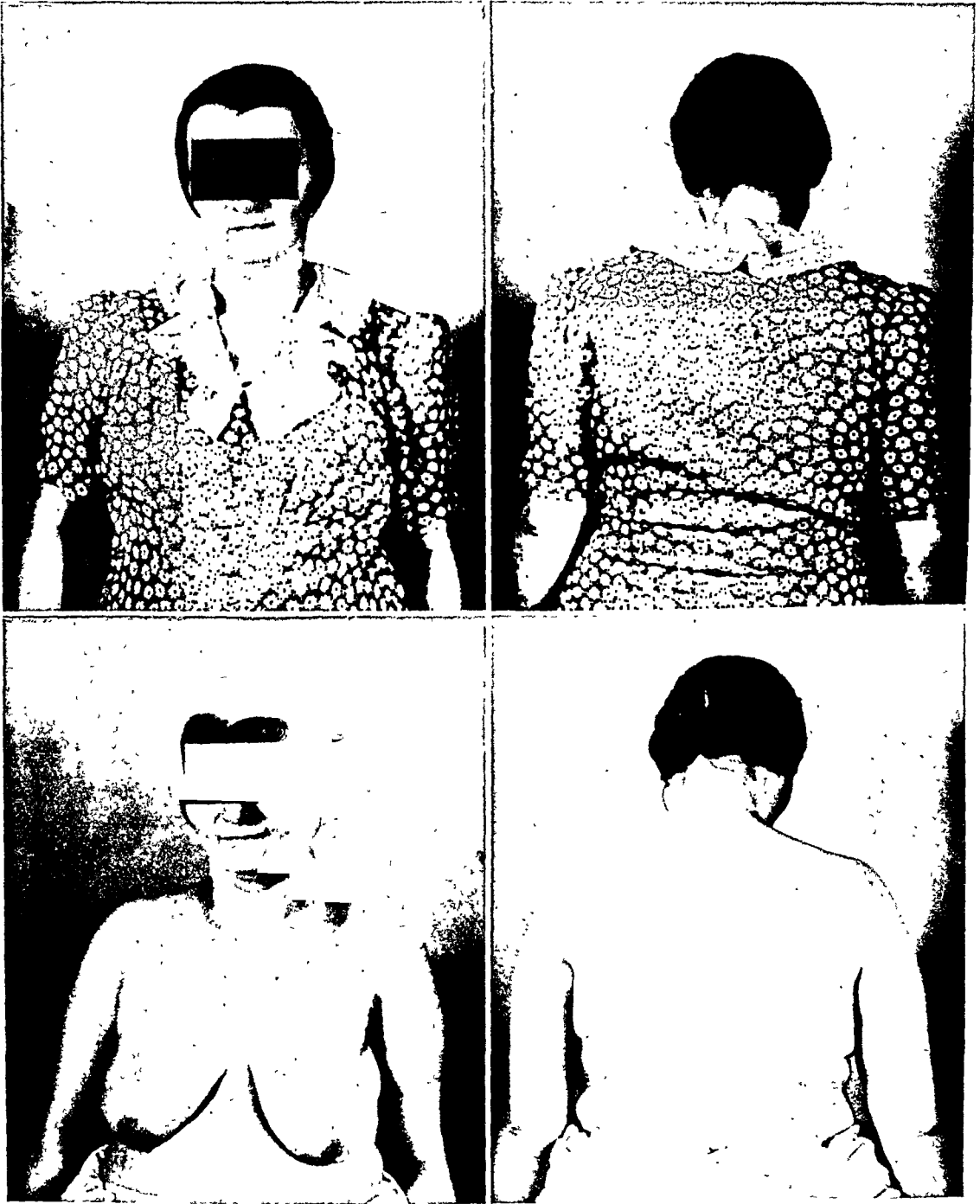


FIGURE 3C

Photographs of Mrs. M. P. (See figures 3A and 3B.) Case #65 in table S. Note absence of deformity, particularly position of shoulder girdle and lack of cervical or thoracic scoliosis.

a minimal inactive lesion. Another patient had had an evanescent minimal lesion three months prior to resection. This had entirely cleared by the time pneumonectomy was performed. Three patients had moderately advanced lesions in the contralateral lung. One patient had a contralateral pneumothorax at the time left upper lobectomy was performed. The remaining patient was one who had bilateral upper lobe giant cavities. A program of bilateral upper lobectomy was planned and recently has been completed. Contralateral lesions were considered to be unstable in 5 and inactive in the remaining 17 patients. Of these 22 patients with contralateral disease, 16 were treated by pneumonectomy and 6 by lobectomy.

The follow-up of these patients has shown that 18 of them have had no contralateral exacerbation. This includes 3 patients whose contralateral lesions preoperatively were considered to be unstable. The following is a description of the remaining 4 patients:

1: A fifteen-year-old female was treated with right pneumonectomy. Three months before the operation this girl had an evanescent exudative lesion in the extreme left apex which had entirely cleared at the time resection was performed. This patient remained well and negative for eighteen months. At this time she developed an acute tuberculous pneumonia in her left upper lobe which was rapidly progressive and caused death within four weeks.

2: A thirty-nine-year-old white female was treated by left pneumonectomy. Preoperatively the X-ray films revealed a very small inactive infiltration far out in the third interspace in the right lung. She was completely well for the first eight months and the X-ray films during this time revealed no contralateral spread. Eight months following resection, however, the X-ray films showed a new lesion developing just adjacent to the previous involvement. This progressed for the first two months and since then has been retrogressive; at the present time it is a fairly stationary lesion. This patient is consistently negative on all tests, including examination of the concentrated sputum, of the bronchoscopically aspirated specimen and the gastric specimen.

3: A fifty-four-year-old white male in extremely poor general condition who had been quite ill for four weeks prior to operation and was still running fever at the time resection was performed. He had a marked fibrous stenosis at the orifice of the left main bronchus, with total destruction of the left lung by tuberculosis and an associated anaerobic infection. He had a minimal lesion in the right apex and first interspace and, during the week prior to resection, developed râles over the right lower lobe and suggestive infiltration at the base. He was classified as a desperate risk and resection was performed; it was realized that this offered him his only chance to live. This patient had a slowly progressive contralateral lesion during the first four weeks postoperatively; it then spread more rapidly, and on the fifty-third day he died of infection and pulmonary insufficiency.

4: A fifty-three-year-old white male was treated by right pneumonectomy. Preoperatively, he had a minimal lesion in the second interspace on the left side. Postoperatively, this lesion appeared to have fuzzier edges and was less well defined. Although it never increased in extent, it has been classified as a questionable contralateral exacerbation because of the change in appearance. Since that time this lesion has become quite fibrotic in appearance. The patient is clinically well and has a negative sputum on concentration.

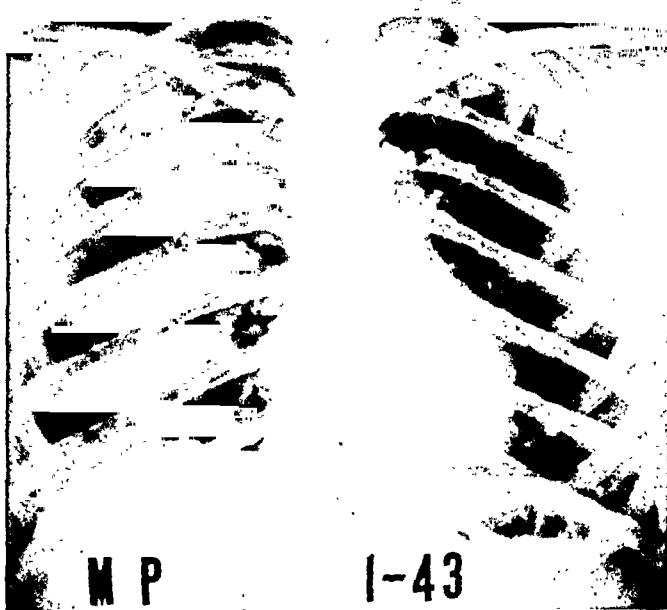
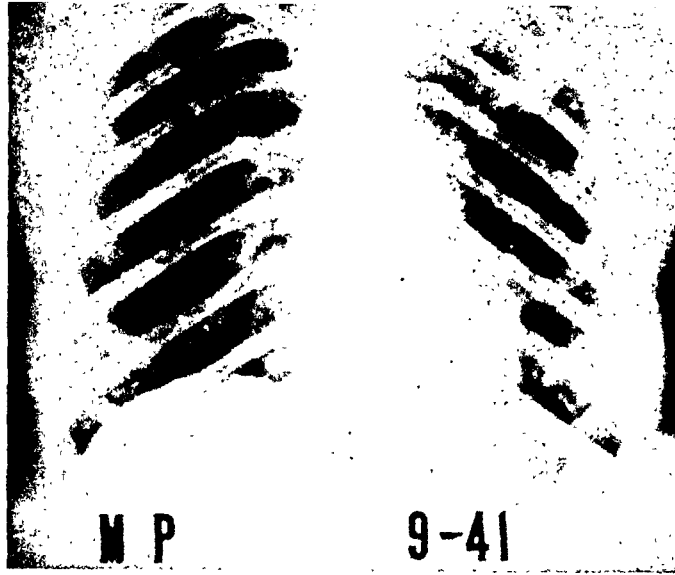


FIGURE 4A



FIGURE 4B

Surgical specimen (left upper lobe) showing the extensive involvement of the apex with a residual slit-like cavity filled with caseous material. The following is the pathological report: "On cut section apical half of lobe contains numerous yellow nodules varying from few mm. up to 0.5 cm. in diameter. These are surrounded by thin gray membrane. Only occasional similar nodule found in lower half. Remainder of lung tissue atelectatic. Also in upper half there is a collapsed cavity 3.5 x 0.5 cm. filled with yellow caseous material."

FIGURE 4A

Miss M. P. Age twenty. Refer to case #43 in table 8 for details.

Upper: Roentgenogram in September, 1941, showing an active exudative lesion in the left upper lobe with a 2 cm. cavity in the first interspace.

Centre: Roentgenogram in January, 1943, after sixteen months of bed-rest and phrenic paralysis. There has been definite clearing, but a dense homogeneous lesion with residual cavity remains at the apex. Sputum positive.

Lower: Roentgenogram in July, 1943, five months following left upper lobectomy. There is no evidence of residual parenchymal disease.

Note: Resection in this case was an elective operation. It was performed in preference to thoracoplasty or a trial of pneumothorax. Her sputum has been consistently negative on all tests including guinea pig inoculation. She is asymptomatic and has returned to normal activities.



In summary, it can be said that 18 of the 22 patients who had contralateral lesions prior to resection have had no indication of contralateral exacerbation. Two patients have died as a result of contralateral exacerbation; one in the post-operative period and one eighteen months following resection. The remaining 2 patients who had contralateral exacerbation, as described above, are clinically well and have consistently negative sputa.

#### POSTOPERATIVE SPREADS

As stated earlier in this paper, postoperative spread remains the greatest threat to the tuberculous patient coming to pulmonary resection. It occurred in 7 patients, or 11.6 per cent of the present series. The fate of these 7 patients was as follows: One patient died on the fifth postoperative day of a contralateral tuberculous pneumonia. Two patients have progressive contralateral disease; at the present time both these patients have positive sputum. One has a receding contralateral lesion and a small cavity. This patient likewise has a positive sputum (Gaffky IV). Another has had marked clearing of the contralateral lesion; this has been stationary now for many months. This patient has a consistently negative sputum on all tests, including examination of the gastric specimen and guinea pig inoculation. The contralateral spread in the remaining 2 patients followed a very interesting and unusual course. Both had considerable spread on the first postoperative film taken within three days following resection. In one, this had entirely cleared within three weeks and, in the other, within six weeks. Both of them are well and their sputa are consistently negative on all tests, including guinea pig inoculation.

As the previous table on complications has shown, the incidence of contralateral spread is almost the same for those treated by pneumonectomy as for those treated by lobectomy. In our opinion, postoperative spread is due to bronchial spilling at the time of operation and is in no way related to the type of operation performed. It is most likely to occur in those who have large amounts of secretion at the time of resection.

In summary, it can be said that postoperative spread has occurred in 11.6 per cent of the patients. It has caused postoperative death of one and will eventually cause the death of 3 more. The prognosis of the remaining 3 appears to be good.

#### THE PROBLEM OF POSITIVE PLEURAL FLUID

Three patients have been accepted for resection who had pneumothorax complicated by pleural fluid in which tubercle bacilli were demonstrated by guinea pig inoculation. Two of them also had tuberculous bronchitis. One patient following resection developed an empyema caused by *Staphylococcus aureus*. At the time the empyema was drained, pleural fluid was collected for study and biopsy of the pleura was taken. The biopsy revealed no evidence of tuberculosis, and the pus from the pleural cavity was negative for tubercle bacilli on concentration and guinea pig inoculation. A thoracoplasty has since been performed on this patient to obliterate the empyema space, and she is clinically well at the

present time. The second patient's convalescence was uneventful. She was clinically well and her sputum was negative for nine months following the resection, at which time she developed a bronchial fistula and a tuberculous empyema. The empyema was drained, and at the present time the bronchial fistula is being treated by cauterization with sodium hydroxide. The third case is clinically well and has a consistently negative sputum. However, he has continued to form a small amount of fluid since the time of resection and has required several thoracenteses. On one occasion the pleural fluid was found to be positive. On all other examinations it has been negative. This patient has not required a pleural tap for the past six weeks, and at present there is no evidence of accumulation of fluid. The presence of a positive pleural fluid is certainly an additional hazard, but should not be considered in itself a contraindication to resection. All 3 of these patients described were treated by pneumonectomy.

#### EXTENT OF RESECTION

The amount of lung tissue to be resected is a matter of prime importance. It depends on two main factors: (1) the extent of the parenchymal disease, and (2) the presence of bronchial disease. It must be remembered that pulmonary resection is being performed to remove all disseminating foci of tuberculosis. It is not sufficient to remove the most evident offending lesion and leave behind less extensive, but nevertheless potentially dangerous, foci of infection. The complete conversion of the sputum is a prerequisite of success in this form of treatment of tuberculosis, as it is in all other forms of therapy. Our experience to date has shown that the resection of too little, and not too much, pulmonary tissue may be responsible for an unsatisfactory result.

When the main bronchus or the orifice of one of the lobar bronchi is involved with tuberculous bronchitis, pneumonectomy can be decided upon prior to operation, as it is absolutely essential to remove these foci. Frequently, however, the extent of resection cannot be finally decided upon until the chest is opened and the lung palpated. It is difficult to determine by palpation whether or not a lesion is active, and one must rely more upon the extent of the disease. Not infrequently considerable involvement is found in one of the lobes in which it was not suspected by X-ray study. The superior division of the lower lobe is notorious in this respect.

From a purely technical standpoint, it is usually possible to perform lobectomy if this is desirable. In only 2 instances have we found the tuberculous involvement extending directly across the fissure line so that lobectomy was impossible. In such cases one is faced with the possibility of doing either a pneumonectomy or a segmental type of lobectomy. At times, in the presence of an undeveloped fissure on the right, we have elected to do a double lobectomy (that is, upper and middle or lower and middle) rather than develop the fissure line by cutting across pulmonary tissue.

Pathological study of the surgical specimens has revealed that, almost without exception, there is extensive involvement of the superior division bronchus when a cavity is present in this segment of the lower lobe. Frequently this involve-

ment extends throughout the course of the bronchus, and the adjacent main bronchus is involved with a submucosal or more advanced type of tuberculosis. In such cases, regardless of bronchoscopic findings, the presence of a marked tuberculous bronchitis of the superior division bronchus must be assumed. This presents a hazard to lower lobectomy in such cases. On the right side, it would seem more advisable to perform a right middle and lower lobectomy, so that the suture line through the bronchus can be placed at a higher level, and increase the chances of getting above the disease.

#### THE PROBLEM OF ACTIVE DISEASE IN THE LUNG TO BE RESECTED

The presence of active, spreading disease in the lung to be resected is not a contraindication to resection. In fact, it frequently is the indication for resection. We do not agree with those who claim that the patient must have established a so-called immunological balance before operation is performed. This concept has deprived many patients of their only chance to get well, as often many of them continue to progress and fail to establish the immunological balance at any time. Complications, such as empyema, bronchial fistula and implantation of the infection in the incision, have not been encountered more frequently in such patients, as was suggested by Churchill and Klopstock (2). Contrary to this, we have found tuberculous granulation tissue in the chest wall of only 3 patients. All 3 had been on sanatorium regimen for many months, and 2 of them had been treated by pneumothorax.

#### TECHNICAL CONSIDERATIONS

Resection of lung tissue involved with tuberculosis is dispatched with greater ease than any other group of patients coming to pulmonary resection. To date, no tuberculous patient has come to resection in whom the operation was not technically possible. Regardless of how adherent the costal pleura may be, as soon as this portion is mobilized the mediastinal surface is usually found to be relatively free, and the lack of adhesions and induration is quite remarkable. Hilar lymph nodes are usually small, the tissue planes are well preserved and the marked fixation of the hilar structures commonly associated with suppuration and tumor is rarely seen.

Individual ligation of the hilar structures is always used. In our opinion, the tourniquet is an instrument which should never be used by the surgeon performing resection for tuberculosis. Individual ligation technique can be applied to either lung or to any of the various lobes, including the left upper lobe. The individual ligation of the hilar structures of the left upper lobe offers no unusual technical difficulties.

The bronchus is closed with silk sutures. When technically feasible, only end-sutures are used. When additional support is desired, a row of mattress sutures is used also. A pleural flap is then developed from the posterior chest wall and reflected over the bronchus. It is sutured into the end of the bronchus.

The meticulous and atraumatic handling of pulmonary tissue, particularly that part which is to remain in the case of segmental resection or lobectomy, is

an important technical consideration. Individual ligation of the hilar structures and the pleural flap method of closing the bronchus are the key notes to success in resection of tuberculous lung tissue.

#### THE PROBLEM OF ENDOBRONCHIAL TUBERCULOSIS

The evaluation of the condition of the bronchial tree is of utmost importance prior to resection in all tuberculous lungs. An endobronchial lesion, either active or inactive, has not been considered a contraindication to resection. On the contrary, it has often been considered as an indication for resection. It must be considered in determining the extent of the pulmonary resection, as ideally both the parenchymal and the bronchial foci should be removed.

Nineteen, or 31.7 per cent of this resection series, had bronchial lesions visible through the bronchoscope. These were classified as follows: submucosal involvement in one, ulceration in 5, ulcero-stenosis in 9 and fibrostenosis in 4. These bronchial lesions were distributed as follows: 4 involved the right upper lobe orifice, one the right main bronchus, 2 the right intermediate bronchus and one the right upper and right intermediate bronchus, 10 the left main bronchus and one the left upper lobe orifice.

The position of the bronchial suture line with reference to the preëxisting bronchial lesion is a matter of interest and importance. Judged by bronchoscopy, the suture line was above the bronchial lesion in 5, immediately adjacent to it in 10 and below it in 4.

Thirty-five patients have been bronchoscoped since operation. Five have been found to have ulceration in the bronchial stump. Four of these patients were treated by pneumonectomy and one by a right lower lobectomy. The incidence in patients bronchoscoped is 14.3 per cent, and for the entire series of 60 patients is 8.3 per cent. In all 5 of the patients who developed ulceration of the bronchial stump, the bronchial suture line had to be placed in or immediately adjacent to an active bronchial lesion. The stump ulcers have been treated, as previously stated, by application of 30 per cent silver nitrate at two-week intervals. Three have been controlled and one patient still has ulceration with positive sputum, but she has failed to return for regular treatment. The remaining patient who had an ulceration of the stump of the right lower lobe bronchus has been treated by further resection. Her bronchial lesion failed to respond to local therapy.

During the past year Dr. William Meissner (4) has studied the problem of endobronchial tuberculosis in the surgical specimens submitted to him following resection. This has been a painstaking piece of work, and has been performed in the following manner: at the time of resection a small segment of the main bronchus is reamputated to provide tissue for study. Then, from the surgical specimen, sections are taken from the remaining portion of the main bronchus, from each of the lobar bronchi, and from each of the segmental bronchi of the various lobes. This study has revealed that tuberculous bronchitis originates in the small bronchi draining the parenchymal foci, extends toward and may eventually involve the main bronchus. Thus, in all cases where involvement

of the main bronchus is found, lobar and segmental bronchi have likewise been found to be involved. Unfortunately, 6 of the small bronchial segments which were taken immediately adjacent to the suture line were lost. Of the remaining 30 pneumonectomy specimens examined, 15, or 50 per cent, revealed tuberculous involvement. The main bronchus was involved in 20, or 56 per cent, of the 36 pneumonectomy specimens. Of the 24 lobes examined, 4 showed tuberculous involvement of the lobar bronchi. Forty-three of the 60 specimens showed involvement of the segmental bronchi. This is an incidence of 71.6 per cent. It is of interest to note that only 12, or 50 per cent, of the 24 lobes showed segmental involvement, whereas 31, or 86.1 per cent, of the 36 pneumonectomy specimens showed involvement of the segmental bronchi. This would indicate the greater severity of the disease in those treated by pneumonectomy. Such a high incidence of bronchial involvement would seem to indicate that the tuberculous involvement of the segmental bronchi is almost universally associated with parenchymal tuberculosis.

The importance of this pathological study is quite evident. It indicates that the main bronchus is involved much more frequently than has ever been suspected by bronchoscopy. It also establishes the fact that bronchial sutures have been placed in involved tissue in many instances. In spite of this, ulceration has occurred only in 5 cases. The important clinical fact is that the bronchial closure remains intact in spite of the presence of tuberculous bronchitis. This has been demonstrated since there has been only one fistula in this entire series of cases. It is true even in those who developed ulceration in the stump. None of these 5 patients developed fistula.

#### RESECTION AS PREFERRED TREATMENT

In a previous paper (5) the types of disease in which resection should receive preferential consideration were outlined. The following quotations from that paper also represent our convictions to-day.

"Although it may be unwise to outline specific indications for an operation which has evoked so much controversy, our experiences prompt us to consider resection as the treatment of choice for the following types of disease:

- 1: In preference to thoracoplasty in cases with active parenchymal disease complicated by bronchial stenosis.
- 2: Extensive basal tuberculosis with or without associated bronchiectasis.
- 3: In unilateral disease that has failed to respond to a pneumothorax with apparently adequate collapse.
- 4: In unilateral disease that has failed to respond to an adequate thoracoplasty.
- 5: In preference to cavernostomy in the treatment of tension cavities in unilobar or extensive unilateral disease.
- 6: In extensive unilobar disease with dense opacities and little evidence of fibrosis and retraction.
- 7: Progressive unilobar or unilateral tuberculosis in the teen-age group.
- 8: Tuberculoma."

## CONCLUSION

Pulmonary resection is an effective and reasonably safe form of treatment for tuberculosis in patients in good general condition. It also salvages some of the desperate risks who otherwise face an imminently fatal issue. The present results have been obtained in spite of the fact that the vast majority of patients accepted for resection have been those with extensive or complicated forms of tuberculosis.

In our opinion, pulmonary resection will be applied in the future to more patients and will find its true place as a supplementary and not a competitive form of treatment to the already established methods of rest and collapse therapy. It will undoubtedly become an elective procedure in certain types of disease. It will also find a widening field of usefulness in the complicated forms of tuberculosis in which collapse therapy has been found to be relatively ineffective or dangerous.

Any report on pulmonary resection as a form of treatment for tuberculosis must be considered as a preliminary report at this state of our knowledge and experience. Because of the nature of the disease being treated, time and rigid follow-up of these patients will eventually tell the true story.

However, enough experience has already been gathered to show that many of the complications and failures in the past have been due, not to tuberculosis *per se*, but to improper technique, the poor selection of patients and, in many instances, to the removal of too little lung tissue. Although the preservation of function is an ideal to strive for and is frequently attained by resection, there are times when tuberculosis, like cancer, must be extirpated at the sacrifice of some functional lung tissue.

The addition of pulmonary resection to our armamentarium in the treatment of tuberculosis places an even greater challenge before clinicians. It is now more important than ever to recognize certain patterns of tuberculosis that respond best to certain types of therapy and fail to respond to others. Only in this way can we apply the proper treatment and avoid serious complications. The old trial and error method of treating pulmonary tuberculosis is no longer justifiable. Complication and failure of other methods should be anticipated on the basis of experience and proved clinical observation.

Pulmonary resection should be used not as a last resort, but before extension of disease and complications have occurred. The earlier it is performed, the greater the possibility of conservation of pulmonary function and the greater the chance of cure.

## SUMMARY

1. Results have been presented for 60 consecutive pulmonary resections for tuberculosis performed between January 1, 1942 and January 1, 1944. There were 36 pneumonectomies and 24 lobectomies.

2. Resection of the tuberculous lung usually is accomplished with greater ease than in cases of pulmonary suppuration or malignancy.

3. Individual ligation of the hilar structures and the meticulous closure of the bronchus with silk sutures and a reinforcing pleural flap have almost eliminated bronchial fistula and empyema as complications.

4. Contralateral spread remains the greatest hazard in pulmonary resection for tuberculosis.

5. Ulceration of the bronchial stump occurred in 8.5 per cent of the patients. This can be diagnosed only by routine bronchoscopy following resection. It may occur early or late in the postoperative period.

6. Active tuberculosis in the lung to be removed is not a contraindication to resection. Waiting for stabilization of the lesion frequently robs these patients of their only chance to get well.

7. Tuberculous bronchitis, either active or inactive, is not within itself a contraindication to resection. It is often an indication for resection.

8. A contralateral lesion is not a contraindication to resection unless it is uncontrolled or uncontrollable.

9. The total operative fatality is 11.6 per cent. The operative fatality in the 47 "reasonable risk" cases is 4.3 per cent and in the 13 "desperate risk" cases is 38.5 per cent.

10. When the patient is in good general condition, the operative fatality for lobectomy and pneumonectomy is almost identical.

11. Pulmonary resection should be considered as a possible method of treatment in outlining therapy for tuberculous patients. Ideally it should be applied before extension of disease and complications occur.

#### SUMARIO

1. Preséntanse los datos relativos a 60 enfermos consecutivos en los cuales se ejecutaron resecciones pulmonares por tuberculosis entre el 1° de enero, 1942 y el 1° de enero, 1944, comprendiendo 36 neumonectomías y 24 lobectomías.

2. La resección del pulmón suele ser realizada con mayor facilidad en la tuberculosis que en los casos de supuración o malignidad pulmonar.

3. La ligadura individual de los tejidos hiliares, el cierre meticuloso del bronquio con suturas de seda y el colgajo pleural de refuerzo casi han eliminado la fístula y el empiema como complicaciones.

4. La propagación contralateral continúa siendo el riesgo máximo en la resección pulmonar por tuberculosis.

5. En 8.5% de los enfermos sobrevino ulceración del muñón bronquial que sólo puede diagnosticarse mediante la broncoscopia sistemática después de la resección, y puede presentarse al principio o hacia el fin del período post-operativo.

6. La tuberculosis activa del pulmón por extirpar no constituye una contraindicación de la resección, pues mientras se espera a la mira de la estabilización de la lesión se priva frecuentemente a esos enfermos de su única probabilidad de restablecerse.

7. La bronquitis tuberculosa, ya activa o inactiva, no constituye en sí misma una contraindicación de la resección, y a menudo representa una indicación.

8. La lesión contralateral no contraindica la resección a menos que no esté controlada o sea incoercible.

9. La mortalidad operatoria total fué de 11.6%, representando 4.3% en los 47 casos de "riesgo razonable", y 38.5% en los 13 casos de "riesgo desesperado".

10. Cuando el enfermo se encuentra en buen estado general, la mortalidad operatoria es casi idéntica para la lobectomía y la neumonectomía.

11. Al bosquejar la terapéutica para los tuberculosos, debe considerarse la resección pulmonar entre los tratamientos posibles, e idealmente debe aplicarse antes de que se difunda la enfermedad y sobrevengan complicaciones.

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#### DISCUSSION

*Dr. Henry D. Chadwick, Waltham, Massachusetts:* I have had the opportunity to read Doctor Overholt's paper and I have seen several of the patients included in this series. His analysis of the results shows that the hazards of empyema and bronchial fistula have been largely overcome and the operative mortality reduced to a degree that gives pulmonary resection a standing as a method of treatment of advanced pulmonary tuberculosis that we clinicians should welcome as a means of saving some otherwise hopeless cases.

The advances made in operative technique, in anesthesia and in chemotherapy have made lobectomy and pneumonectomy so much safer that, when other methods fail to control the disease, we should not hesitate to recommend them.

Instead of stressing the mortality from pulmonary resection, we should keep in our minds that, out of 60 pulmonary resections, 53 were successfully performed; that, out of 46 patients classed as reasonable risks, only 3 were unsuccessful and, of these, 32 have a good prognosis and negative sputum, 9 others a guarded prognosis and only 3 are listed as in poor condition.

These cases have had what might be called standard methods of treatment and some of them were in sanatoria for years and the resections were done only as a last resort. Under these circumstances, this high salvage rate is a credit to the operator and gives us another offensive weapon to use in the treatment of pulmonary tuberculosis.

The patients we should refer to the thoracic surgeon for resection are the following types:

First, those with bronchial tuberculosis with stenosis which makes pneumothorax or thoracoplasty inadvisable.

Second, cases with thick-wall and tension cavities that cannot be collapsed by pneumothorax or thoracoplasty.

Third, patients in whom thoracoplasty has been performed, but who continue to raise



positive sputum and in whom bronchoscopic examinations and X-ray studies make it reasonably certain that the bacilli come from the operated side.

Fourth, patients with extensive, productive disease, with or without bronchiectasis, especially basal lesions.

Preferably, the above cases should be unilateral, but, even if there has been some slight involvement of the contralateral lung and the disease is retrogressive or stable, resections are not contraindicated.

The danger of contralateral spreads remains a menace and occurred in 12 per cent of Doctor Overholt's cases. We know, however, that such spreads frequently occur in advanced pulmonary tuberculosis after thoracoplasty, pneumothorax or when only bed-rest is carried out. Therefore, this possibility should not deter us from an operative procedure when it is indicated.

It is important, it seems to me, that a resection, either a lobectomy or a pneumonectomy, should be followed by a modified thoracoplasty to obliterate the space left by the resection. Otherwise, in lobectomy, overexpansion of the remaining lobes, if they contain tuberculous foci, might cause activation of the disease and, in pneumonectomy, emphysema of the remaining lung would occur that would decrease the respiratory reserve if this precautionary measure were not taken.

*Dr. J. Maxwell Chamberlain, Cooperstown, New York:* My discussion will be limited to one phase of this problem: namely, upper lobectomy.

When disease is limited to the upper lobe and conservative measures have failed, we frequently resort to two forms of therapy: a selective thoracoplasty or an upper lobectomy. In a report a few years ago Doctor Overholt found the modern selective thoracoplasty successful in converting the sputum in 90 per cent of the cases and the fatality rate in this series was less than 3 per cent. The operation was unsuccessful therefore in 7 per cent of the cases. Recently I reviewed 46 consecutive modern selective thoracoplasties with a partial scapulectomy for disease limited mainly to the upper lobe, and found that the operation converted the sputum in 80 per cent of the cases (concentrate examination). The fatality rate was less than 2 per cent. From these figures and others in the literature, it is safe to say, therefore, that the disease in an upper lobe will be controlled (from a pathological point of view) in from 80 to 90 per cent of cases and the few failures can still have a lobectomy with probably less risk, because after a thoracoplasty the sputum contains fewer organisms, is diminished in amount and, should an empyema occur, the pleural space is reduced in size and the problem simplified.

Consideration must also be given to the pulmonary dynamics subsequent to either of these procedures, since little has been gained by a bacteriological cure if the patient becomes a respiratory cripple. Physiologists teach us that the diaphragm and lower six ribs are mainly responsible for the ventilatory burden, while the upper lobes contribute comparatively little. The loss of function by a selective thoracoplasty may therefore not be great in an upper lobe already partially destroyed by disease. In 12 patients with selective six-rib thoracoplasties on whom bronchspirometric studies were done by Wright and Woodruff before and after operation, it was found that 3 patients showed a reduction in function, 6 patients showed no significant change and 3 patients showed improvement. In 25 per cent, then, there was some reduction in function and in 75 per cent there was no significant change. We know less about respiratory function after lobectomy but I should like to review 3 cases on whom Doctor Wright was good enough to do bronchspirometric studies.

First, may I show the functional studies on a typical six-rib selective thoracoplasty with

a partial scapulectomy. His maximum minute ventilation is 89 liters, his vital capacity 2.5 liters, and his divided function shows that the right lung (thoracoplasty) is doing 47 per cent of the ventilation and the normal left lung 53 per cent. The oxygen consumption on the right is 40 per cent and on the left 60 per cent. In the next patient a mistaken diagnosis of a tuberculoma was made and an upper lobectomy was done without any post-operative complications. Functional studies one year after operation are not quite as good as those in the patient above, though the maximum minute ventilation and vital capacity are about the same, namely, 90 liters and 2.5 liters, respectively. The divided function shows that 40 per cent of the ventilation is being done by the left overdistended lower lobe while the right lung is doing 60 per cent, but the oxygen consumption on the left is only 30 per cent and on the right 70 per cent. The third case is one in which an apical empyema occurred after an upper lobectomy, but responded well to drainage. For six months the wound was healed, the patient was without symptoms and back to full-time work when she began to have pulmonary hemorrhage. Bronchoscopy revealed a kinked right stem bronchus from angulation of the lobe as it ascended into the thoracic vault and a small pea-sized granuloma which was removed with biopsy forceps several times before it completely disappeared. Gradually a shadow appeared at the apex of this overdistended lobe and the patient now has a small pulmonary abscess two years after lobectomy. The maximum minute ventilation is 65 liters, the vital capacity 1,500 cc. and the divided function shows that the minute ventilation on the right is 40 liters and on the left 60 liters; but the oxygen consumption on the right is only 10 per cent and the left is consuming 90 per cent. Ventilation is good but oxygen consumption is poor.

Therefore, if the function after upper lobectomy is not improved over that after a selective thoracoplasty (with a partial scapulectomy) and the rate of sputum conversion remains the same or is lower, it does not seem justifiable to do the more hazardous operation, namely, lobectomy as the initial procedure.

*Dr. John Alexander, Ann Arbor, Michigan:* At present, the following things seem of special importance with regard to pulmonary resection for tuberculosis:

(1) Both lobectomy and pneumonectomy have a definite place in the treatment of tuberculosis and have been used in a number of clinics for more than ten years for patients in whom no other form of therapy offered a reasonable chance of recovery.

(2) Great praise is due to Doctor Overholt and Doctor Wilson for their boldness and the skill they have demonstrated in operating upon and saving certain of the patients whose cases they have just shown to us.

(3) The indications for thoracoplasty are broad and, in my opinion, those for lobectomy and pneumonectomy are narrow. During the last two years I have recommended lobectomy or pneumonectomy for only a small fraction of the number of patients Doctor Overholt has chosen.

(4) The early and late fatality rates and the percentage of postoperative complications in the modern type of thoracoplasty are very low and the percentage of apparent cures is high, even when thoracoplasty is routinely used for many of the lesions which Doctor Overholt believes should be treated by pneumonectomy or lobectomy.

(5) Except for Doctor Maier's remarkable record of only one death (6.2 per cent) among his 16 pneumonectomy and lobectomy patients, I know of no series of cases as large as his in which the early fatality rate is less than Doctor Overholt's, which is 13.6 per cent, and that of the Massachusetts General Hospital's 35 patients, which Dr. Richard Sweet tells me is 11.4 per cent.

(6) The percentage of serious complications after lobectomy and especially after

pneumonectomy is several times greater than that after thoracoplasty. Apparently the most serious and frequent are spread or reactivation of tuberculosis in remaining portions of the lung or lungs. Other potentially serious complications are empyema, broncho-pleural fistula, tuberculous wound infection, tuberculous meningitis and persisting tuberculous infection of the bronchus at the site of its division.

(7) Pneumonectomy or lobectomy only rarely removes all the tuberculous lesions and a disappointingly large number of patients continue to have tubercle bacilli in their pulmonary secretions either from an ulcerated bronchial stump or from new, reactivated or old active parenchymal lesions.

(8) The late fatality rate and the percentage of apparent cures are not yet known in any large series of cases. In view of what I know of the late results in several small series of cases, I believe the late results in large series will be poor.

(9) The loss of function resulting from the removal of a whole lung, or even of only an upper lobe with varying degrees of fixation of the lower lobe from traumatic pleural effusion, is of clinical importance in a disease that is prone to late recurrence of activity.

(10) If, as I believe, the end results of pneumonectomy and lobectomy will prove to be far inferior to those of thoracoplasty in cases in which either type of operation might reasonably be used, I strongly recommend that neither pneumonectomy nor lobectomy be used in preference to thoracoplasty in any case unless the indications for resection are clear-cut and unless thoracoplasty is unlikely to succeed.

# CLOSURE OF THE BRONCHUS IN PULMONARY RESECTION<sup>1</sup>

JOHN C. JONES<sup>2</sup>

The problem of the closure of the bronchus is of paramount interest to surgeons and of the greatest importance with the increasing numbers of pulmonary resections carried out for the treatment of bronchogenic new growth, bronchiectasis, pulmonary suppuration and tuberculosis. The advancement of the technique of bronchial closure has increased the margin of safety of pneumonectomy and lobectomy as evidenced by the decreasing number of complications and fatalities due to postoperative bronchial stump leakage, fistulae and infections.

Rienhoff (1), in his excellent report on his experimental and clinical observations on the closure of the bronchus following total pneumonectomy, concluded: "Finally, it would appear that the most important steps in the procedure to effect solid healing of the bronchus are, first to occlude the amputated stump with as few sutures as will prevent the passage of air long enough to permit sufficient healing of the cuff of the bronchus distal to the suture line; second, to avoid in every way devitalization of the terminal end of the amputation stump; and third, to effect an intimate apposition between the cut end and the surrounding areolar tissue, preferably mediastinal pleura."

Leakage at the suture line and sloughing of the bronchial stump with the resulting bronchial fistula and empyema constitute the major causes of serious complications, morbidity and fatality in pulmonary resection. Therefore, the surgeon must be meticulously careful in the closure of the amputation stump; the bronchial artery must be preserved; the least amount of peribronchial dissection should be carried out proximal to the cut end, with a minimum of soiling of this area during and after amputation; the sutures should be placed and tied with the least amount of trauma to the stump, and the suture line should be airtight before closing it over with surrounding areolar tissue and mediastinal pleura; and last, the suture material must be nonabsorbable and of a type that creates the least tissue reaction in a potentially if not actually contaminated area.

A method of bronchial closure suggested to me by T. E. Jones (2), and which has been used by him, employs over-end interrupted sutures of stainless steel (alloy) wire (35 gauge) incorporated in an atraumatic (intestinal) curved needle. I have found it to be a practicable, simple closure with satisfactory results in 31 pulmonary resections. This closure is described in detail.

After the dissection of the hilum and ligation and severance of the pulmonary vessels, the bronchus with its peribronchial tissue intact is carefully dissected and a curved clamp placed across it at the chosen site of amputation. Another clamp is placed distal to this to prevent leakage and soiling and the bronchus is amputated flush with the surface of the proximal clamp by scalpel (figure 1). Single

<sup>1</sup> Presented before the Medical Section at the 40th annual meeting of the National Tuberculosis Association, Chicago, Illinois, May 11, 1944.

<sup>2</sup> 1136 West 6th Street, Los Angeles 14, California.

over-end wire sutures are placed in the amputation stump from anterior to posterior, approximately three millimeters proximal to the clamp, using eight in number for the average adult main stem bronchus (figure 2). The atraumatic curved needle pierces the bronchus easily if the needle is beforehand lubricated thoroughly with vaseline. All the sutures having been placed, brought out over the clamp and held out in the wound in order and with the least tension (figure 3), the clamp is removed and the sutures tied snugly but not tightly over the end of the bronchus (figure 4). The wire sutures should be tied in a square knot without kinking and must not be tied too tightly because of the tendency of the fine wire to cut through tissue.

Usually the bronchial walls remain in apposition without air leakage while the wire sutures are being tied. Almost always the bronchial artery bleeds when the bronchial clamp is removed. This is ligated with fine silk suture at the end of the bronchus after the wires are tied off. Occasionally, a wire suture occludes the bleeding bronchial artery when it is tied over the end of the bronchus.

The bronchial stump sutured, the pleural cavity and mediastinal raw surface are thoroughly rinsed with saline solution, and, with mild positive pressure applied by the anesthetist, the bronchial stump is tested by inspecting the fluid for air bubbles. Five grams of sulfanilamide crystals are sprinkled over the bronchial stump and mediastinal raw surfaces, then the mediastinal pleura closed with interrupted fine silk sutures leaving an opening at either end for the drainage of serum and the escape of air if a bronchial fistula should develop. In order to obtain enough pleura to cover this area it is usually necessary to dissect and undermine the pleural flaps forward and backward before suturing them. Five grams of sulfanilamide crystals are sprinkled into the pleural cavity and wound and the latter is closed.

We believe this type of bronchial closure has distinct advantages. It is thought that stainless steel creates the least amount of tissue reaction in a potentially infected area. This fine material used on an atraumatic needle makes a small hole at the site of entrance and exit in the bronchial wall, and the sutures being placed at the end of the bronchus do not in any way impede the blood supply of the stump. None of the sutures has sloughed into the bronchus and been coughed up by the patient. This closure allows for a high amputation of the bronchus when a proximally located new growth demands it, and it would be feasible where the bronchus is entirely amputated with a portion of the wall of the lower trachea without the use of the clamp.

The placing of mattress sutures high up on the stump and near the bifurcation of the trachea before amputation is not always feasible and it would appear to be impossible under certain conditions. The application of the bronchial clamp and amputation before suturing are, in our estimation, less conducive to infection than is amputation and then suturing a wide-open, blowing bronchus. There is probably less chance of injury to the bronchial artery suturing the end of the stump than in other methods where more proximally placed mattress sutures are employed. We have seen no complications or infections attributable to the use of the crushing clamp at the end of the bronchus. Ochsner (3) and

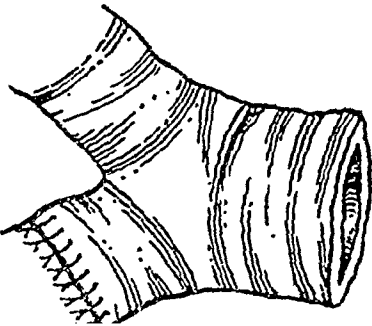
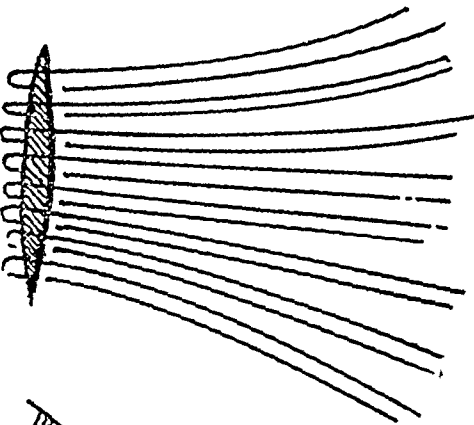
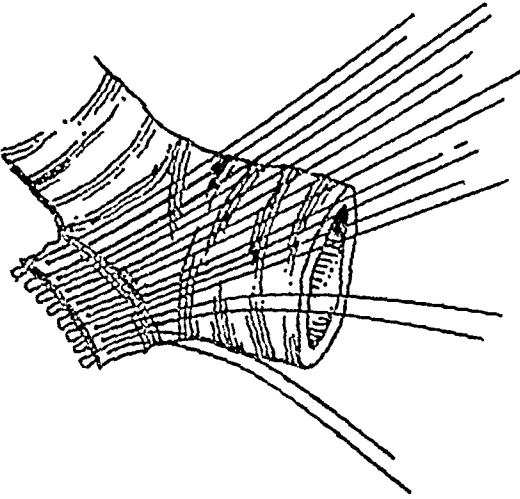
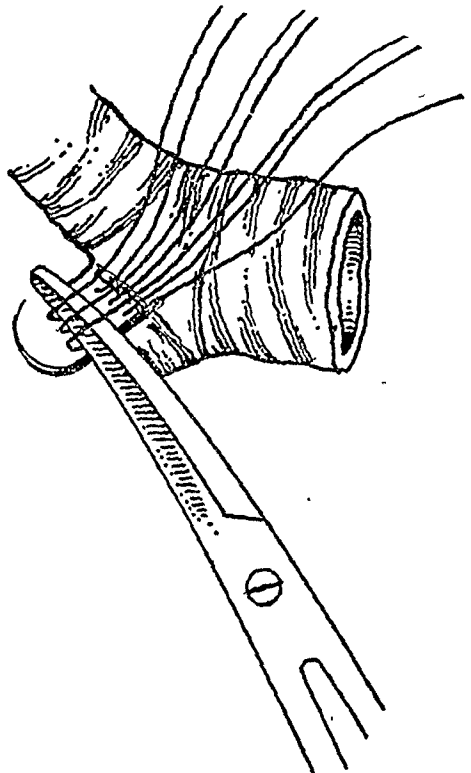
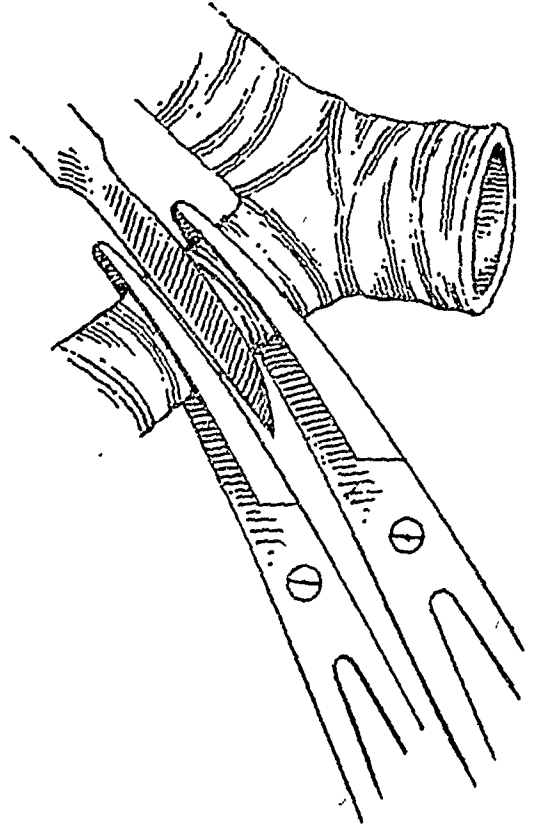


Fig. 1. (Upper left)

Fig. 2. (Upper right)

Fig. 3. (Lower left)

Fig. 4. (Lower right)

The bronchus is amputated between clamps.  
 The bronchial stump is sutured over the clamp with interrupted steel wire sutures.  
 The sutures are all placed before the clamp is removed.  
 Wire sutures tied over the end of the bronchus.

Shenstone (4), in their discussion of Rienhoff's report, both stated they routinely employed the clamp to the bronchial stump without any apparent complications.

We employ the same method of bronchial closure in lobectomy and partial lobectomy as in pneumonectomy, having found it to be equally as effective. The dissection and ligation of the vessels having been accomplished, the amputation and closure of the bronchus are left to the last when the lobe is amputated between curved clamps.

Since the success or failure of pulmonary resection depends a great deal upon the bronchial closure and since the incidence of empyema with or without bronchial fistula may be directly attributed to the healing of the bronchial stump, we have tabulated our results in 18 pneumonectomies (table 1) and 13 lobec-

TABLE 1  
*18 pneumonectomies*

NUMBER OF CASES	REASON FOR PNEUMONECTOMY	EMPHYEMA	FISTULA	DEATHS
12	Carcinoma	2 } (22%)	1 (5.5%)	1*
2	Bronchiectasis			
2	Abscess	2 }	0	1†
1	Arteriovenous fistula			
1	Adenoma			

\* Heart failure, no empyema or fistula.

† Bronchopneumonia.

TABLE 2  
*13 lobectomies*

NUMBER OF CASES	REASON FOR LOBECTOMY	EMPHYEMA	FISTULA	DEATHS
9	Bronchiectasis	9		
2	Abscess	2	1 (7.6%)	1*
1	Cysts (infected)	1		
1	Adenoma	1		

\* Died four weeks postoperatively of toxemia and infection.

tomies (table 2) from the standpoint of the incidence of empyema and bronchial fistula in our entire series in which the type of bronchial closure described above was used.

In the series of 18 pneumonectomies (table 1), 4 patients developed empyema, but only one (5.5 per cent) had a demonstrable fistula; 2 of the 4 were operated for carcinoma and they both recovered following drainage; one required thoracoplasty to obliterate the empyema, though his bronchopleural fistula had closed promptly after drainage. Two empyemata complicated pneumonectomy for multiple lung abscesses, neither of which had bronchial fistula. One of these patients died on the seventh postoperative day. Autopsy revealed an intact bronchial stump sealed off, an empyema and deep wound infection, but his death was attributed to a pneumonia of the entire remaining lung due to a spill-over of

large amounts of purulent secretion during the operation. He was cyanotic and had a wet lung at the completion of the operation. The remaining empyema has a residual pocket and may require thoracoplasty. One of the 12 pneumonectomies for carcinoma, in fact the twelfth patient in this series, died on the ninth postoperative day of persistent auricular flutter and heart failure, autopsy revealing a healing, sealed-off bronchial stump and clean pleural cavity. The 2 pneumonectomies for bronchiectasis healed *per primam*; one was done for extensive tuberculous bronchiectasis with positive sputum, and the other was found to be infected with bovine actinomycosis, as found postoperatively in the excised specimen. In the entire series of 18 pneumonectomies there were 2 (11 per cent) hospital deaths, neither of which was due to infection or bronchial fistula.

All the lobectomies (table 2) developed empyema but this cannot be attributed to the bronchial closure for we drain all lobectomies with either an intercostal tube or by rib resection with air-tight tube drainage. Only one patient (7.6 per cent) had a bronchial fistula, that in a fifty-year-old male with multiple

TABLE 3  
31 resections

NUMBER OF CASES	TYPE OF RESECTION	EMPYEMA	FISTULA	DEATHS
18	Total	4	1*	2†
5	Two-lobe	5	} 6.4%	} 9.6%
2	Lobe and lingula	2		
6	Single lobe	6	1	1

\* Recovered after thoracoplasty.

† One died of bronchopneumonia and one died of heart failure.

chronic putrid lung abscesses, who had been ill in the hospital for many months; he demonstrated poor healing qualities despite much vitamin therapy and chemotherapy, he had a wide-spread virulent and foul wound infection; a progressive, large sloughing area of the chest wall developed about the wound and he died of toxemia four weeks after surgery. Lobectomy was done as a last resort despite his poor preoperative condition. None of the empyemata following lobectomy has required thoracoplasty to obliterate the pocket.

Thirteen lobectomies (table 3) were completed with one death (7.6 per cent). There were 5 two-lobe, 2 lobe plus lingula, and 6 single lobe resections in this series. All were one-stage procedures. The only bronchial fistula developed in a patient with a single lobe resection; the multiple lobe resections developed none. The incidence of bronchial fistula would seem to be higher in lobectomy (7.6 per cent) than in pneumonectomy (5.5 per cent), but this series of cases is too small to draw conclusions. The covering over of the bronchial stump with pleura in pneumonectomy is invariably more satisfactory than in lobectomy in our experience, and we believe this to be an important factor in the development of bronchial fistula as pointed out by Churchill, Rienhoff and others.



## SUMMARY

1. A simple, practicable closure of the bronchial stump in pneumonectomy and lobectomy has been presented.

2. It has the advantages of utilizing a suture material that creates a minimum of tissue reaction in a potentially if not virtually infected area; one that seals off the bronchus air-tight until healing of the bronchial stump has taken place, without impairment of the blood supply to the very end of the stump.

3. The bronchus is kept closed throughout the process of amputation and suturing, minimizing the chance of contamination of the field by bronchial secretions and blowing air from the open bronchus.

4. This method is not proposed to be the ideal, but, in our experience, it has been the best procedure for closing of the bronchus thus far attempted. A higher amputation of the bronchus can be accomplished with less interference with blood supply, leaving a short cuff of bronchus for repair.

5. The incidence of bronchial fistula, empyema and mortality in 31 pulmonary resections is reported.

## SUMARIO

1. Descríbese una técnica sencilla y práctica para el cierre del muñón bronquial en la neumonectomía y la lobectomía, que posee las ventajas de utilizar para sutura un material que produce un mínimo de reacción histológica en una zona potencial sino virtualmente infectada; y de que cierra herméticamente el bronquio hasta que tiene lugar la cicatrización del muñón sin afectar el riego sanguíneo hasta el mismo extremo del muñón.

2. El bronquio permanece cerrado durante todo el proceso de la amputación y la sutura, mermando así las probabilidades de contaminación del campo operatorio por las secreciones bronquiales y por el aire que penetra por el bronquio abierto.

3. No se propone esta técnica como ideal, pero al autor le ha resultado ser la mejor hasta ahora para el cierre del bronquio, pues permite amputarlo más arriba con menos interrupción de la circulación, y dejando para reconstrucción un brazaletes de bronquio.

4. Preséntase la incidencia de la fístula bronquial, el empiema y la mortalidad en 31 resecciones pulmonares.

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## DISCUSSION

*Dr. Willard Van Hazel, Chicago, Illinois:* The origin of this excellent paper lies in the universal problem confronting those attempting pulmonary resection, particularly pneumonectomy where the consequences of an open bronchus are serious complications.

Doctor Jones has arrived at his conclusions because this method in his hands has more nearly satisfied the requirements which Rienhoff proposed and which are generally accepted as sound.

There are two reasons, in my opinion, why this method deserves serious consideration. First, the results attest to its effectiveness. Second, it is based on sound surgical principles.

In the removal of an esophageal diverticulum we are confronted with the closure of the neck without the aid of a protective serosal covering which makes stomach and intestinal anastomosis a relatively safe procedure. Therefore, a meticulous closure with the swedge needle or arterial needle is employed to limit trauma to a minimum. This same care is needed in the closure of the bronchus. I have observed, on the introduction of the needle into the bronchus, an escape of a bubble of air and have consequently reduced the size of my needle and suture material. I now use a number 12 twisted silk suture which qualifies in strength for this purpose. The sutures are placed much as Doctor Jones has placed his over the end of the bronchus. However, when desirable one or two mattress sutures are placed in the bronchus just above this closure. In other words, the bronchus is cut at different angles in different cases, and I have found it preferable to apply appropriate sutures according to the needs of the individual case rather than following a fixed pattern.

Some time ago a patient with a carcinoma of the right upper lobe required a high amputation of the bronchus which included a part of the wall of the trachea. The closure was effected over the endobronchial tube introduced into the left main bronchus for anesthesia. At the completion of the closure I was impressed with the retraction of the stump into the mediastinum. Then the mediastinal pleura with the azygos vein which is not cut served most adequately to cover the stump. Since then I have employed a high amputation, though not as extreme as this, and find that, if the mediastinal pleura is incised close to the lung posteriorly, superiorly and anteriorly, it is adequate to completely cover the stump. This is accomplished by a continuous fine catgut suture after washing the wound with saline and applying three grams of sulphathiazole crystals to the root bed and later three more into the pleural space.

This procedure has been carried out in 15 cases: 6 carcinomata, one sarcoma, 3 multiple abscesses, 3 tuberculosis with bronchial lesions, one bronchiectasis and one traumatic atelectasis (fracture of the bronchus).

There were 2 deaths, one in a man with a known heart lesion operated for carcinoma, who after an uneventful convalescence developed pulmonary edema on the twelfth post-operative day and died in six hours. The other death was in a patient with multiple lung abscesses who developed edema of the lung and died on the second day, though his condition had not been good since his surgery. Autopsy in both instances confirmed the cause of death and showed a good sealing of the bronchus by the mediastinal pleura.

One patient, in whom the amputation had not been high and the stump only partially covered, developed a fistula for three days when it closed spontaneously. Five cases developed empyema, 2 of which were draining from the lung at the time of their pneumonectomy. One, a tuberculous patient with a stenotic bronchus, raised 1,400 cc. of sputum following dilatation of the bronchus. Another with multiple abscesses was raising 1,000 cc. prior to drainage. In each case the hazard of large amounts of sputum seemed too great for a primary pneumonectomy. In the other 3 patients who developed empyema, no fistula existed at any time. The amount of suppuration within the lung, adhesions and their extent, the necessity for handling the lung are some of the factors which determine a complicating empyema without the presence of a bronchial fistula. Penicillin may decrease its incidence in the future.

# BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS<sup>1</sup>

## III. Chronic Fibroid Phthisis—Chronic Productive Tuberculosis

B. A. DORMER, J. FRIEDLANDER AND F. J. WILES

The technique employed in this study was in the first few cases that of previous papers (1, 2, 3). It occurred to the senior author, in the course of the work, that it might be interesting to try the effect of various medicaments suspended or dissolved in the radiopaque oil on the bronchial tree. Sulphonamide powder was first tried in minute quantities and it was discovered that no ill effects resulted. Consequently we became bolder and bolder until as much as 2 g. of sulphonamide powder was suspended in each 5 cc. of lipiodol. A change to sulphadiazine followed with equally innocuous results.

The pictures obtained on bronchography appear to gain in contrast giving an almost three-dimensional appearance to the bronchial system, and the patients, although their sputum was increased for the first day or so following the instillation of the dual medium, stated that there was a marked decrease in following days.

We were then emboldened to try the effect of repeated instillation of sulphonamide powder suspended in lipiodol in this particular form of pulmonary tuberculosis (chronic fibroid phthisis). To our surprise and gratification we found that 3 cases who had had positive sputa for years became negative and we have therefore adopted this dual procedure of diagnosis and therapeutic medication in all subsequent cases.

The unexpected result also led us to initiate more experiments. First, cases before thoracoplasty had the diseased side filled with sulphonamide lipiodol suspension three days before operation and we have since had a series of 5 consecutive cases whose postoperative course has been smoother in all respects than any other series hitherto operated on by our team.

We then applied the method to septic conditions of the lung, such as lung abscess, in the chronic stage of which we treated 2 cases with dramatic results, and in bronchiectasis which appeared to improve considerably, but we have had too little experience with the latter conditions to be able to dogmatize.

Chronic fibroid phthisis (chronic productive pulmonary tuberculosis) is, in our experience, a trying and difficult type of tuberculous disease to treat. Nearly all the carriers of the disease appear to be in this class and many of them never realize that they have been disseminating tubercle bacilli for many years until they have an hemoptysis or they have their sputa examined by an enthusiastic doctor because they complain of catarrh or "smokers' cough." When discovered, these cases form a difficult administrative problem because they are apt to feel well after a short period of rest but continue to have positive sputa for many years, in fact for the normal span of life. Treatment seems almost impossible because of the almost universal bilateral nature of the

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condition, its extent and the low vital capacity and dyspnea which accompany its chronic existence.

This type of case is apt to fill hospital beds for many years and block the institution with limited accommodation from admitting early and perhaps other treatable types of tuberculosis. Yet, when discharged, persons suffering from chronic fibroid phthisis can live a normal span of life and continue to act as the source or reservoir of infection for countless persons. Like the typhoid carrier and the diphtheria carrier, they are a menace to public health and because they do not feel ill they resent any incarceration or isolation.

In the majority of cases it appears to us that the basic disease is bronchial block followed by atelectasis, pneumonitis and subsequent excavation or bronchiectasis, resulting ultimately in a distorted, twisted and diseased bronchial tree which continues to pour tubercle bacilli from the ulcerated, dilated or cavitated areas for many years.

The cases which follow illustrate in detail this condition. in what we hope to be a self-evident manner.

#### CASE REPORTS

*Case 1:* E. 561, European male aged fifty-one years, commercial traveller. He had always been healthy except for dry pleurisy in 1928 and again in 1930. Two weeks before his admission to the hospital in January, 1942, he had a sudden hemoptysis, about half a cupful of blood. Since then he had had a cough with a little sputum but otherwise had felt well.

On admission to the hospital he appeared fit, temperature was normal and he had not lost weight. Clinically he had signs of cavitation at the apex of both lungs. Sputum contained tubercle bacilli. A conventional X-ray film showed a classical example of chronic fibroid bilateral phthisis. Bronchography was performed in order to demonstrate the exact nature of the apical lesions. The two sides were done on different days and no complications occurred.

Figure 1, taken with the patient lying down, shows the bronchogram of the left side. The basic condition has probably been a block of the left upper lobe bronchus. Note how well the bronchiectatic cavities are drained by large open bronchi and the distortion of the left main bronchus. Figure 2 was taken with the patient standing up. Note the pooling of the lipiodol in the main bronchus and that the streaking in the first plate is in keeping with the elongated and distorted bronchi. Essentially similar conditions were revealed by a bronchogram of the right upper lobe.

Patient has been working at his old occupation of commercial traveller for two years. During this time he has felt quite well, there has been no recurrence of the hemoptysis and his sputum has remained consistently positive.

*Case 2:* C. 303, colored female, aged thirty-four years, housewife. She had a pleurisy (right) in 1936. She was quite fit from then until eighteen months ago, when she developed a cough. Three weeks before admission, cough became really troublesome and she was X-rayed for the first time at an Anti-Tuberculosis Clinic which she visited on her own initiative.

She was admitted to King George V Hospital on February 23, 1943. She was a healthy-looking thin woman with no obvious signs but with a positive sputum. A conventional

FIG. 1



FIG. 2



FIG. 3

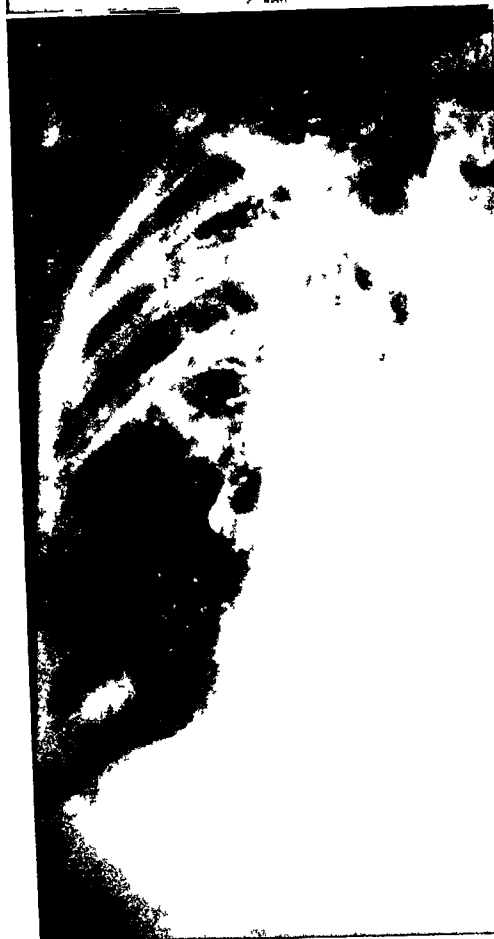


FIG. 4



FIG. 5



FIG. 6

X-ray film showed chronic fibroid phthisis of the left upper lobe and some suspicious mottling in the right infraclavicular region.

A bronchogram (figure 3) showed the crowding together of the left upper lobe bronchi and their termination in cavities, the consequent upward pull of the left main bronchus, the distortion of the lower lobe bronchi accounting for the streaking on the conventional film. A bronchogram of the right side showed only minor bronchiectasis.

This patient appeared to have less sputum a few days after the initial bronchography so it was decided to treat her with therapeutic instillation of sulphonamide powder suspended in lipiodol. She had two instillations into each lung and lay on the treated side with a downward tilt for some hours after each treatment. Following this, her sputum became negative after many years of positive findings. This is only six weeks since the last instillation, but appears to be significant because of the repeated appearance of tubercle bacilli in all previous specimens.

*Case 3:* E. 425, European female, aged twenty-eight years, housewife. She had pleurisy with effusion on the left side in 1935 and was seven months in bed. She was perfectly well and healthy after the pleural effusion and married in 1936. In 1938 her only child was born and she felt quite well during the pregnancy. In August, 1939, she had "flu" and coughed up "a spot of blood." In October, 1940, she developed a troublesome cough and was diagnosed as having pulmonary tuberculosis in January, 1941. In February, 1941, she was admitted to King George V Hospital.

On admission her general condition was very good. Her temperature was 97 to 99.2°F. She had cough and sputum which contained tubercle bacilli on direct smear. Physical examination showed impaired percussion note and bronchial breath sounds at the left apex posteriorly. A roentgenogram showed mottling in the left apex and infraclavicular region and thickening of the pleura at the left base.

A bronchogram showed that the lesion was a bronchiectasis of the left upper lobe.

A one-stage thoracoplasty (four ribs) was done with permanent conversion of the sputum.

*Case 4:* E. 621, European female, aged thirty-four years, teacher. Onset of her present illness was in 1928 with temperature and dry cough. She was in Brompton Hospital for two months and then in Frimley Sanatorium for three months. A right artificial pneumothorax was done here and maintained for fifteen months. In 1933 cough returned and after prolonged rest in bed she came to South Africa in 1935 where she had rest treatment until 1941, when she felt well enough to take up a teaching post which she occupied until January, 1943, when she had a sudden large hemoptysis.

She was admitted to King George V Hospital on October 5, 1943. Her general condition was poor, she was dyspneic; vital capacity was 1,200 cc., sputum positive, temperature 100°F. There was dulness and flattening of the right chest, crepitations over the upper lobe and distant bronchial breathing. A roentgenogram showed a blacked out right upper lobe with deviation of the heart and trachea to the right.

A bronchogram (figure 4) shows that the right upper lobe consists of a series of bronchiectatic cavities with marked deviation of the trachea to the right and distortion of the rest of the bronchial tree. The mediastinum and heart are shifted to the right. The probable origin of the condition has been an atelectasis of the right upper lobe.

A first-stage thoracoplasty was preceded by the application of sulphonamide powder in lipiodol to the bronchi three days before the operation. In spite of the poor general condition and low vital capacity, the postoperative course was completely uneventful.

Sputum still is positive. Patient will have further instillation of sulphonamide-lipiodol and a second-stage thoracoplasty, if necessary.

*Case 5:* E. 393, European female, aged thirty-five years, housewife. She was quite well until seven months ago when she began to get frequent colds. On October 28, 1941, she had a sudden hemoptysis of one cupful of blood. She called her doctor who had her X-rayed. She was admitted to King George V Hospital on November 24, 1941, with positive sputum.

On admission her general condition was good. Her temperature was normal. The only physical signs were a few crepitations at the right infraclavicular region on coughing and deep inspiration. A chest film showed mottling of both apices and infraclavicular regions with streaky markings to the diaphragm.

A bronchogram (figure 5) shows the bronchiectasis of the left upper lobe with the marked upward pull of the left main bronchus and the distortion of the rest of the left bronchial tree.

Sputum remained consistently positive and it was decided to instil sulphonamide suspension in lipiodol on several occasions on both sides. This was done, both sides receiving two applications at intervals of two to three weeks. Sputum was lessened considerably and is negative on direct smear, but is still positive on concentration of a twenty-four-hour specimen.

*Case 6:* E. 564, European male, aged thirty-two years, factory hand. He had a right-sided pleurisy fourteen years ago. Then, he was quite well until six months ago when he started to cough—a slight morning cough with little sputum. He was admitted to the hospital seven weeks ago with an acute appendicitis and, following operation, his temperature did not come down and his chest was X-rayed and tuberculosis diagnosed.

He was admitted to King George V Hospital on September 11, 1941. His general condition was fair, his sputum positive and temperature was elevated to 101°F. After some months of rest his condition improved, his sputum became negative and he was discharged on January 31, 1943.

He was readmitted on February 9, 1943, because he had a large hemoptysis two days after discharge, while travelling in a bus on a long cross-country journey. His sputum was positive. An X-ray film showed some mottling of the right apex and infraclavicular region.

In view of the excellence of his general condition and the fact that there were no physical signs, a bronchogram was done. This (figure 6) shows that the mottling of the right apex is caused by a bronchiectatic upper lobe.

The patient has had several treatments with sulphonamide powder suspended in lipidol and sputum is now consistently negative. In view of hemoptysis, patient has requested a thoracoplasty and this will be done.

*Case 7:* E. 388, European male, aged forty-four years, purser. He remembers coughing for two years and this has been his only symptom. He had an acute appendicitis in October, 1941 and, following the operation, the cough was aggravated so he consulted his doctor who diagnosed tuberculosis.

He was admitted to King George V Hospital on May 11, 1942. He weighed over 200 lbs., was a healthy-looking man with normal temperature. Sputum was positive. Physical signs were those of a cavity in the right upper lobe. A roentgenogram showed a blacked out right upper lobe and a great increase in the lung markings on this side. The trachea was deviated to the right.

A bronchogram (figure 7) shows a bronchiectatic upper lobe (most probably following atelectasis) and marked tracheal shift to the right. There is distortion of the rest of the bronchi.

A two-stage thoracoplasty was performed with no change in the sputum. He then had two applications of sulphonamide lipiodol suspension to the bronchiectatic area and his sputum is now negative on direct smear but positive on twenty-four-hour concentration.

*Case 8:* E. 388, European female, aged sixty years, widow. This patient gave a history of cough and sputum for many years, but she had never worried about this until three months before admission when she became short of breath.

On admission her general condition was poor. Temperature was 97 to 99°F. Sputum was positive. Physical examination showed an emphysematous chest with dullness and coarse crepitations over the left upper lobe. She had tachycardia with irregularly recurring ventricular extrasystoles.

Figure 8 shows old-standing disease of the left upper lobe with shift of the mediastinum, heart and trachea to the left. There are some healed lesions in the right upper lobe. A bronchogram (figure 9) (patient lying down) shows the bronchiectasis of the left upper lobe with marked upward pull of the left main bronchus and distortion of the rest of the bronchial tree. Note the extreme deviation of the trachea. Figure 10 was taken with the patient standing up. Note the pooling of lipiodol in the distorted left main bronchus.

Patient gradually became worse in spite of strict bed-rest and died some months later.

*Case 9:* E. 549, European male, aged fifty-four years, clerk. He has had what he terms a "cigarette cough" for many years, but has never felt ill. In his youth he was an Olympic runner and represented his country in the 100-yard race. He became hoarse some months ago and consulted his doctor who had him X-rayed. He worked until the day of admission.

When he arrived in the hospital he looked well, his temperature was normal and the only physical signs were a few crepitations in the infraclavicular region. Sputum was positive. A chest film showed old-standing lesions in the right apex and infraclavicular region and some mottling in the left apex and infraclavicular region.

A bronchogram (figure 11) shows that the essential disease is a right upper lobe bronchiectasis.

No change occurred after a year of bed-rest. He will be treated with instillations of sulphonamide in lipiodol.

*Case 10:* C. 13, colored male, aged twenty-eight years, farm hand. He had "flu" in 1936 and right-sided pleurisy. He was kept in the hospital two weeks. Four months later he complained of cough and sputum and spent fifteen months in a sanatorium. On discharge (April, 1938) he felt well and went back to work.

He was admitted to King George V Hospital in January, 1939, because of cough and deterioration of general health. On admission his general condition was good. His temperature rose to 99°F. in the evenings. Sputum was positive. Physical signs were impaired percussion note and crepitations over the right upper lobe. A film showed an old-standing lesion in the right apex and infraclavicular region and marked streaking on this side with tenting of the right diaphragm.

A bronchogram (figure 12) shows the essential lesion to be a bronchiectasis of the right upper lobe with marked deviation of the trachea and distortion of the right bronchial tree.

The patient remained well for some months until he had a sudden hemoptysis resulting in extensive spread of the disease and death.



FIG. 7



FIG. 8



FIG. 9



## SUMMARY AND CONCLUSIONS

1. Ten cases of chronic fibroid phthisis are described. Such patients often are the innocent carriers of tubercle bacilli and are discovered only by the accident of hemoptysis.

2. Bronchography in each case has illustrated the essential lesions much more clearly than conventional radiography. The essential pathological development seems to follow the course:

bronchial block—atelectasis—pneumonitis—  
 bronchiectasis } —distortion of bronchial tree.  
 excavation }

3. Much use has been made of a suspension of sulphonamide powder in lipiodol, both in diagnosis and treatment.

4. It is suggested that this suspension may sterilize chronic bronchiectatic areas and cavities in cases of pulmonary tuberculosis in which the sputum has been positive for many years. These cases form a difficult administrative problem and any procedure which will render them noninfectious is an important advance in treatment.

5. It is suggested that this form of treatment (instillation of sulphonamide-lipiodol suspension into bronchi) should precede major thoracic surgery and that it may form a possible form of treatment for suppurative conditions of the lung.

## SUMARIO Y CONCLUSIONES

1. Describense en este trabajo 10 casos de tisis fibroidea crónica. Esos enfermos son a menudo portadores inocentes de bacilos tuberculosos, que sólo se descubren cuando sobreviene el accidente de una hemoptisis.

2. En todos los casos la broncografía puso de manifiesto las lesiones esenciales con nitidez mucho mayor que la radiografía habitual. La evolución esencial de la patología viene a ser la siguiente: bloqueo bronquial, atelectasia, neumonitis, bronquiectasis con excavación y deformación del árbol bronquial.

3. Tanto en el diagnóstico como en el tratamiento se ha empleado mucho una suspensión de un sulfonamido pulverizado en lipiodol.

4. Indícase que esta suspensión puede esterilizar zonas y cavernas bronquiectáticas en los casos de tuberculosis pulmonar en que el esputo ha sido positivo por muchos años. Esos casos plantean un difícil problema administrativo, y cualquier procedimiento que los convierta en no infecciosos representa un adelanto importante en el tratamiento.

5. Indícase que este tratamiento (instilación intrabronquial de una suspensión de sulfonamido-lipiodol), debe preceder a toda cirugía torácica mayor y puede ofrecer una posible forma de tratamiento en los estados supurados del pulmón.

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## TUBERCULOSIS IN WARTIME

HARLEY WILLIAMS<sup>1</sup>

Tuberculosis can destroy the finest human material in every nation. Yet all modern knowledge shows that this disease, if fought with medical and social weapons known to us now, can be cured and largely prevented. The story of tuberculosis in Britain during this war is one of initial deterioration followed by a much improved outlook.

Britain has had a national tuberculosis scheme since 1912. The doctor's first problem is to find the tuberculosis patient and to give him expert help and handling—he needs both from the medical and social point of view. This, in Britain, is done in special clinics called tuberculosis dispensaries in the charge of specialist doctors known as tuberculosis officers. The earliest tuberculosis dispensary was opened by Professor Sir Robert Philip in Edinburgh as far back as 1887, but, by 1912, tuberculosis dispensaries became general throughout the country, and there are now about 400 of them in England alone.

These dispensaries are centres for diagnosis and treatment. Here, the suspected case of tuberculosis is X-rayed, clinically examined, and the laboratory tests are performed. The first object is to make sure whether or not the patient has tuberculosis and to initiate treatment. But recently, tuberculosis dispensaries have developed the social aspects of their work, chiefly as a consequence of the new allowances in money now paid to patients. These will be described more fully later.

The tuberculosis dispensary also handles the examination of contacts—especially children and young adults who have been living or working near the patient and who may have been infected by him with the germ of the disease. Contacts are X-rayed and examined with the tuberculin test and kept under careful observation for years, since the risk of their developing tuberculosis is many times greater than in an ordinary person. Specially trained nurses called health visitors look after the patients' home conditions. The tuberculosis officer supervises patients on their return to ordinary life after being in the sanatorium and assists them to obtain suitable employment and housing accommodation. Artificial pneumothorax and artificial sunlight are given at the tuberculosis dispensary. In fact, the care of the patient as a whole goes on here.

These tuberculosis dispensaries are controlled by the local health authorities, some 120 in number throughout England. From them, patients needing treatment are sent to sanatoria also managed by the health authorities who have developed an elaborate scheme of clinics, sanatoria, hospitals, workshops open-air schools and special centres.

There are now approximately 485 tuberculosis dispensaries in England and nearly 30,000 beds for the treatment of such patients.

Naturally, the Tuberculosis Schemes differ in detail in the 120 local authority areas. For instance, the Lanchashire County Council (covering a population

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of two million) is divided into 9 dispensary areas, employs 18 specialist doctors and has 1,110 beds. The London County Council (responsible for a population of four million) has 2,781 beds for treatment.

The dispensary services have, however, been maintained not far below their peacetime level, but this means longer hours for all the staff. The greatest threat to the welfare of tuberculosis patients and to the clinical work of the doctors has come through deficiency of sanatorium beds. This is partly due to reservation of hospitals for war casualties, and partly to an acute shortage of nursing and other personnel. The position has improved since the supply of nurses was taken in hand by the Minister of Labor, but it still remains difficult.

The death rate from tuberculosis (all forms) increased in 1941 by 13 per cent over 1939. For nonpulmonary tuberculosis the increase was 21 per cent. This increase was greater than in the first Great War. We need not search too deeply for the cause of this increase. It is a phenomenon common to all wars, in which overstrain, anxiety, dispersal of population play a part.

Another unexpected trend has occurred in the first two years of war, the increase of childhood tuberculosis has been proportionately greater than the general increase. This may partly be due to evacuation of children to homes where an unsuspected case of pulmonary tuberculosis was able to infect them. The trend has drawn attention once again to the essentials in preventing childhood tuberculosis. Children are always infected from adults. This contact may be difficult to discover and remove, but the tuberculin skin test (Mantoux) is very helpful in finding the infected child and, of course, every adult person with a chronic cough is encouraged to have X-ray examination and sputum tests.

A Special Committee of the Medical Research Council, a Government organization which supervises medical research, was set up under the well known English physician Lord Dawson of Penn, to investigate the wartime increase and has made far-reaching recommendations. As a result of this report, it can be said that in the future the tuberculosis service will be in a very much better position to handle its responsibilities, and this improvement paradoxically is the direct consequence of the war.

The most significant proposals of the Special Committee are mass radiography and special financial provisions to enable tuberculous people to give up work in order to undergo treatment. Although intended to meet the wartime conditions, these measures are certain to be continued into peacetime.

The most spectacular development in wartime tuberculosis work, mass miniature radiography, is a method of examining the heart and lungs which has been made possible by the modern camera using a high angle lens. Mass radiography, of course, is much cheaper than taking hundreds of full-sized films, and these miniature pictures give a general indication of whether the chest is normal or not, and whether a large film is desirable for more adequate inspection.

Mass radiography is not a method of final diagnosis and must not be treated as such. But it enables the population of a school, a factory, or even a whole area to be examined quickly and cheaply. It is largely in use throughout the fighting services. A number of specially designed X-ray units are being manu-

factured and are in use throughout Britain. Two of the sets are to be sent to Russia by the British Ministry of Health (in replacement of two already sent but unfortunately lost at sea).

Each X-ray unit needs a permanent team of one doctor and five technical assistants. Experience of preliminary work suggests that, out of every 100 presumably healthy people so examined, 7 or 8 will need to come back to the doctor for a large-size X-ray film and clinical examination, 3 will have some chest or heart disease requiring further investigation, and less than one will have pulmonary tuberculosis. Over 1,000 people can be comfortably examined in one week by each unit, which is fully mobile and can be, if necessary, set up in half an hour.

Through mass radiography many latent cases of tuberculosis, with few or even with no symptoms, are being discovered. The method will be quickly developed after the war when more X-ray equipment is available.

Financial allowances recommended by Lord Dawson's Special Committee are now paid by the health authorities to all tuberculosis patients who have a prospect of returning to work after treatment. They are intended to support the wife and dependents of the patient while he is in the hospital and therefore not earning. In addition to a standard allowance there are extra payments for special circumstances (such as extra rent, school fees, exceptional commitments) and of course the patient does not pay for his treatment, though a slight reduction is made in the standard allowance when he is resident in a hospital. These financial allowances are made on the recommendation of the tuberculosis officer after a careful assessment of the patient's clinical condition, and are in the first instance for six months but can be renewed for further periods. The only condition is that the patient must be prepared to carry out the tuberculosis officer's advice on treatment. There is no "means test" for the standard allowance. The patient receiving these allowances is now able to carry on his cure with the minimum of worry on account of family responsibilities.

Although the clinical methods of treating tuberculosis have improved so much during the last twenty years, more progress has still to be made in bringing the patient back into a mode of living which suits the state of his health. This process of gradual readjustment we call rehabilitation. Tuberculosis is a slow, chronic disease. It impairs will-power more than most diseases; it may produce the chronic invalid who is a drain on his family and the community and often a danger to others.

Many patients are recovered in the clinical sense and leave the hospital with their disease arrested, yet they are not fit for heavy work, or for the job they followed before the illness. On the other hand, many tuberculosis people even with actual symptoms, such as a chronic cough, can lead useful lives and do many hours of work in a factory, provided they have medical care, and provided, for the protection of others, that precautions are taken against the spread of infection. It is good for the patient to feel he is not an outcast but is capable of taking his part. Handling such patients presents problems.

Village settlements, such as Papworth and Preston Hall, provide the best

opening for a number of these patients. A sanatorium is in the centre of the village and there are houses, communal centres and factories, where many hundreds of tuberculous men and women live among their families and manage whole industries, such as printing, manufacture of wool and leather products, etc. For the patient who finds life in such a community congenial, this is an ideal solution of the personal problem.

Many tuberculous patients, however, prefer to be out in the world and not kept apart with other semi-invalids. The new Disablement Act passed in 1944 places the men and women who are incapacitated by tuberculosis in exactly the same position as regards employment as a soldier wounded in war. When this Act is fully put into operation, there will be more village settlements and special workshops for tuberculous people and the number of them will be absorbed into industry on the same footing as those incapacitated by war injuries.

The full development of these schemes will occur only after the war. But in time it will be possible to give the tuberculous patient, from the moment of diagnosis to the day of his cure, complete and social care. This is an ideal towards which tuberculosis workers have looked for thirty years.

We are still searching for a chemotherapeutic agent that will do for tuberculosis what salvarsan did for syphilis, and sulphapyridine and penicillin have done for acute diseases. Research is going on and, although no such remedy has been found for tuberculosis, it is possible that any day a new drug may be discovered that will enable us to control the pathological process inside the human body.

Until that day comes, we must rely on the older and slower methods: rest in the open air, pneumothorax and special treatments combined with nursing and good nutrition.

Early diagnosis through X-rays, with attention to the psychology of our patients and concern for their social welfare on completing treatment—this is the modern outlook on this ancient disease.

The outlook for the eradication of this disease is good. With an era of peace and relative prosperity, we should in Britain be able to reduce it to a minor problem in the space of a generation.



Florence B. Seibert

THE CONFERRING OF THE NATIONAL ACHIEVEMENT AWARD<sup>1</sup>  
UPON DR. FLORENCE B. SEIBERT AT THE WHITE HOUSE,  
OCTOBER 6, 1944

The Scientific Achievements of Dr. Florence B. Seibert

ESMOND R. LONG<sup>2</sup>

It is a pleasure and a privilege to discuss the scientific work of Dr. Florence B. Seibert. She has received many awards for distinguished service. The first one came to her twenty years ago. It was the Ricketts Prize of the University of Chicago, and, although her work for most of the succeeding years has been on tuberculosis, this award came for achievement in a quite different field. It was for discovery of the cause of an obscure type of fever that occasionally follows the injection of supposedly pure solutions into the veins of men and animals. Doctor Seibert and an associate discovered that this unusual fever is due to the presence of certain bacterial protein products in the distilled water employed in preparation of the solutions used.

The award on that occasion was a money prize, and Doctor Seibert made use of it in a quite unexpected manner. She did not celebrate, as she was entitled to do, nor did she put the proceeds into some necessary piece of scientific apparatus, as many thought she might. Instead she bought herself a new pair of legs. At least that is the way she put it to me. She purchased an automobile, which enabled her to overcome the handicap that had been so serious for nearly all her life. It was not easy, under the physical circumstances, to learn to control this new apparatus, wholly different from anything she had ever tried before, but characteristically she mastered it, as she has mastered all her problems since.

Since then she has made many important discoveries. I shall discuss just three of them. The first one, and perhaps the best known, was the isolation and purification of the specific protein principle of the tubercle bacillus. In 1924 she joined a team of workers banded together under the auspices of the Committee on Medical Research of the National Tuberculosis Association, and engaged in an extraordinarily intimate analysis of the germ of tuberculosis. In passing, it may be said that her work has been recognized by this Association in the form of continuous support since that date. In the succeeding years she isolated the active principle of the important substance tuberculin. It was an exceedingly arduous task, requiring enormous industry, as well as great chemical skill. It was years before the product was completely purified. She had left the University of Chicago, where she began her research work on this sub-

<sup>1</sup>The National Achievement Award is a gold medal which is awarded, by Chi Omega, annually to an American woman of notable accomplishment in the professions, public affairs, arts, letters, business and finance, or education. It was founded in 1930.

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stance, and pursued the problem further at the Henry Phipps Institute of the University of Pennsylvania. Finally, because of the growing recognition of the importance of a highly purified product for standardization purposes, she was asked by the National Tuberculosis Association and the United States Public Health Service to prepare the substance on a large scale for use as a national standard.

With the aid of facilities in a commercial firm, Sharpe and Dohme, Inc., which coöperated with the National Tuberculosis Association, she isolated 100 grams of the extremely potent product, enough material to give five billion tuberculin tests. The chemical operation was a very delicate one, much of which had to be carried out in a cold room at a temperature not much above freezing. Doctor Seibert and her associates, bundled up in furs, worked in that room for days at a time, isolating the precious material.

Because of the war, expected arrangements for making the product the international standard have not been consummated. However, it is informally accepted, the world over, as the standard product.

In later years Doctor Seibert discovered that this product itself could be still further purified, if more modern and refined methods were used in its preparation. In order to learn these methods she went to Upsala, Sweden, to acquire facility in the new physico-chemical methods of the distinguished Swedish chemist Svedberg. She received a Guggenheim Fellowship for this purpose. She returned with a new set of principles and new concepts which she put to work in further refinement of the product. Elaborate apparatus was required, which was supplied by the Carnegie Corporation.

The second and third discoveries to which I shall make reference were an outgrowth of the new method she had developed. Both were concerned with changes brought about by tuberculosis in the blood. The blood contains three proteins, two of which, albumin and globulin, are normally in a state of balance. This balance is not infrequently upset in disease. Doctor Seibert discovered that an imbalance occurs in tuberculosis. She found that the albumin is reduced while various fractions of the globulin are increased. The increase in the latter component, which she observed both in tuberculous rabbits and in the blood of tuberculous men, proved to be of prognostic significance, running parallel with the extent and progress of the disease.

The third discovery was also concerned with the composition of the blood in tuberculosis. It was one of those unusual occurrences that characterize scientific research. In the course of her many studies on the proteins of the blood in tuberculosis, she was constantly struck by the appearance of an abnormal element, which showed up in a characteristic way in the curves produced by the elaborate apparatus she used. A peak in those curves reminded her of a similar peak she had observed in the many preparations of crude tuberculin she had examined. It corresponded, as her analyses had previously shown, to a certain carbohydrate, or sugar-like product, that accompanied the protein of the tubercle bacillus. Finding a similar peak in the curves obtained in her blood analyses, she was led to the bold hypothesis that perhaps she was dealing with the carbohydrate of

the tubercle bacillus. The substance, whatever it was, increased in amount in almost direct proportion to the seriousness of the disease, and it was natural to believe that it might reflect the presence of products liberated by the tubercle bacillus in the body. The actual identification of this unusual and interesting product has not yet been made, and I do not believe that Doctor Seibert now holds that it is derived from the tubercle bacillus itself. The substance is a carbohydrate, intimately attached to the protein of the blood plasma, and it bears a definite relationship to certain immunological characteristics of the serum of the animal or man concerned. There is much work left to be done in the identification of this compound, but there can be no question of its importance.

Mrs. Collins has mentioned the significance of Doctor Seibert's work in relation to tuberculosis as a postwar problem. As she has said, tuberculosis now takes a heavy toll in the countries that have suffered want and severe privation in this long war. It can be said without question that much of Doctor Seibert's work will be of direct importance. In the reconstruction period after hostilities have ceased, surveys will be necessary to determine the incidence of tuberculosis as a community problem. In such surveys tuberculin will be used to determine the index of infection, and whether the purified product is employed or not, it is quite certain that an evaluation of the strength of the product used will be made with reference to the purified product isolated by Doctor Seibert. Her other work will have a less direct but none the less important application, since all scientific work that brings us new knowledge of tuberculosis and enables us to have a better understanding of its nature will ultimately aid in its conquest.

In closing, I should like to say just a few words about Florence Seibert herself. In twenty years of close association with her I have never seen her ruffled, nor, within that time, have I ever known her to admit that she was tired. I have seldom seen one who works so hard. The amount of labor she has performed is almost incredible for one of her frail physique. She has accomplished it with some unusual strength, hard to explain, which appears to be all her own.

## Education and Research

DAVID ALLAN ROBERTSON<sup>3</sup>

"Education and Research" includes consideration of the college, the university, the institute. Recently in our country, institutes like the Rockefeller in New York, the Brookings Institution in Washington and the Institute for Higher Studies in Princeton have been devoted to research without obligation of members to teach. In university graduate schools, professors have pursued research as teaching duties permitted. Under their guidance candidates for the degree of Doctor of Philosophy have carried on investigations and have been expected to continue such independent work afterwards as college teachers, for most of them become members of faculties. At least some colleges encourage their professors to conduct research. It is of the place of research in the college that I wish to speak particularly.

The college can, and some colleges do, encourage research by teachers and students. There is excitement for the student who works beside a biologist who has abolished about a hundred species of fish as the result of his observations not in a laboratory where he could examine specimens from a jar of alcohol but in the deep waters around the Dry Tortugas where, from behind a diver's helmet, he could watch the living fish and find that what had been thought two species were really male and female of one. There is stimulus for a history student who works with a professor who has written the best book in English on the Latin Americas. There is a quickening impulse for a student of literature who is associated with an editor of Sir Richard Steele's Correspondence and his Traits and Pamphlets or with a Pulitzer Prize winner who has published the biography of a famous American. The best college teacher is the leader of an exploring party, not of a Cook's tour.

The college student, if the college encourages its professors to be explorers, will rise to the opportunity and responsibility of exploring. The best colleges to-day select students who have shown evidence of intellectual interest and initiative. They afford the student a chance for guidance by true explorers. It may be that seniors under direction of a professor of Political Science will, as internes in an OPA office, learn ways to improve procedure in handling problems. It may be that, like one American undergraduate woman, a student under supervision of a professor who had been a consultant to South American legations in Washington, a student may choose to work for honors by studying the background of the Chaco dispute and, spending one day a week in the Map Division of the Library of Congress, may find there two ancient manuscript maps pertinent to the dispute and unknown to either of the disputants. The best college student like the best college teacher is a member of an exploring party.

Of course, there has been complaint that much of the research in college and university is futile. Who is to say? Sir Arthur Shipley told me that he had

<sup>3</sup>President of Goucher College, Baltimore, Maryland.

spent large sums in order to drop hundreds of little bottles all over the North Sea. Each bottle was weighted to float at a known level, was dropped at a known point, and contained a printed slip offering a shilling to the finder who reported the time and place of finding. Sir Arthur said that he was savagely ridiculed for useless expenditure of time and money. It was exactly the record of currents thus established that enabled the British Admiralty to mine the North Sea in the last war. It is true that one never can be entirely sure. Even a negative result may be important. The best statement I know on the place of research in university and college is to be found in the recently published book on the British Universities by Sir Charles Grant Robertson, Principal of Birmingham University:

"It is a most sacred and obligatory function of a university to impart knowledge by the best methods, to perpetuate the pursuit of truth by training and grading those really best qualified to pursue it at different stages and to advance knowledge through the independent contribution of its members.

"The only knowledge that is worth advancing is 'related knowledge,' i.e., knowledge of which the affiliations to, and contacts with, all other forms of knowledge are recognized and the total sum of which is purposively related to human ends, the ends of a civilized society seeking to fulfill a spiritual interpretation of life."

During these war years "related knowledge" has been coming secretly to Washington from hundreds of researchers all over the country. We understand the meaning of knowledge related to winning the war. We can almost as definitely know and encourage knowledge related to life in peace—such research as has been conducted by Dr. Florence Seibert. In her we have an inspiring example of the influence of education and research on a person possessed of that native curiosity which leads her to find out about things, encouraged by her college to seek the high character of an explorer, trained by her university to search independently for truth, and afforded by research institutes the opportunity to persist in her efforts to make original contributions to knowledge. Doctor Seibert has shown other researchers the possibility and importance of advancing "related knowledge"—"knowledge related purposively to human ends, the ends of a civilized society seeking to fulfill a spiritual interpretation of life."

## Response of Dr. Florence B. Seibert<sup>4</sup>

I accept this medal as an extremely generous gift to me, and even more as an honor and a stimulus to the work of women, as well as a tribute to science itself. I appreciate the kind remarks of Doctor Robertson, President of Goucher College, the college which started me on my way of life. I appreciate also the generous remarks of Colonel Long, a teacher, colleague and friend, one who has always fostered and helped the work in every way possible and who always raises his associates above themselves by expecting from them the best or even a little more.

Not every girl awakes to her dream of a birthday party in The White House. I believe the last time I was in this first of all houses was way way back when our High School graduating class toured the city. One of our many rules then was, "When you are in The White House, don't ask for something to eat." Little did I then suspect that there would be all this hospitality and graciousness in a later year. A leader among women, our gracious hostess elects to honor a woman and therefore women in general.

I told Doctor Hinkle when she came to see me that it seemed most unfair to put five such leading women on the award committee, thus barring them from becoming recipients.

An award like this, with its emphasis, coming as it does from a group of young women, the Chi Omega Fraternity, to an older woman, is a source of deep appreciation on my part. Would that that spirit which has prompted this gift might permeate throughout all the world of youths! That will to appreciate beauty and truth in every field of endeavor, along with a sportsman-like sense of humor, will be the salvation of this sickened world. May I emphasize that latter trait. I do not believe there would be so many wars if we all had a better sense of humor. It is this trait that makes us love our American boys and it is this trait that will carry them through to victory and then make them reformers rather than oppressors.

Did you ever stop to think that in war the aim of every man, except one, is to win power and subjugate, even to destroy if necessary the enemy. Who is that one man? The doctor. He gives aid to the best of his ability to every man, foe or friend alike. The Hippocratic oath, taken by many physicians when they first enter the profession, is not set aside even for war. Because the oath has been an inspiration to me, I quote it here:

"I swear by Apollo the physician, by Æsculapius, Hygeia and Panacea, and I take to witness all the gods, all the goddesses, to keep according to my ability and my judgment the following Oath:

"To consider dear to me as my parents him who taught me this art; to live in common with him and if necessary to share my goods with him; to look upon his children as my own brothers, to teach them this art if they so desire without fee or written promise; to impart to my sons and the sons of the master who taught me and the disciples who have

<sup>4</sup>Henry Phipps Institute, Seventh and Lombard Streets, Philadelphia, Pennsylvania.

enrolled themselves and have agreed to the rules of the profession, but to these alone, the precepts and the instruction. I will prescribe regimen for the good of my patients according to my ability and my judgment and never do harm to anyone. To please no one will I prescribe a deadly drug, nor give advice which may cause his death. Nor will I give a woman a pessary to procure abortion. But I will preserve the purity of my life and my art. I will not cut for stone, even for patients in whom the disease is manifest; I will leave this operation to be performed by practitioners (specialists in this art). In every house where I come I will enter only for the good of my patients, keeping myself far from all intentional ill-doing and all seduction, and especially from the pleasures of love with women or with men, be they free or slaves. All that may come to my knowledge in the exercise of my profession or outside of my profession or in daily commerce with men, which ought not to be spread abroad, I will keep secret and will never reveal. If I keep this oath faithfully, may I enjoy my life and practice my art, respected by all men and in all times; but if I swerve from it or violate it, may the reverse be my lot."

Shall we train every one to be doctors? I do not mean that there are no evil doctors but what I mean is to emphasize a way of thinking.

I can perhaps speak better for science than for any other field and here the search for truth is the guiding principle, which immediately eliminates all prejudices of race, creed or sex. By science is not meant the greedy hoarding of accumulated facts for the benefit of one industry or nation in competition with another, but the impartial search for truth implied in a doctorate of philosophy. Science taught in this way should make us all good neighbors, for we would realize that the better the conditions of our neighbor and the more facts he can discover, the closer we all will be to the ultimate truth and better conditions will exist for everyone. To be concrete, for example, in my own work the more knowledge concerning proteins, immunological reactions, tissue reactions, epidemiology, etc. that can be accumulated by my colleagues, the sooner will we find a real help for tuberculosis, and it doesn't make the slightest bit of difference in what nation or by whom that information is gathered.

Will we ever come to the realization that knowledge, contrary to a piece of property, is one thing that can be possessed by any number of people without infringing upon each other's rights? In fact, the dissemination of that knowledge tends to make us richer rather than poorer. There is no joy greater than the discovery of some unknown law of nature or some fact which starts a succession of discoveries. Have you watched children in the room of physics in the Franklin Institute? There is no greater need and there can be no greater contribution to civilization than the development of this way of thought in our youths. If the young Nazi heads had been crowded with this way of thinking, war and all they have done would be as distasteful to them as it is to our boys who must stop this joyful way of life now to prevent destruction of all that is worth while for all time. If Hitler's ambitions had not been frustrated in his youth by his father and he had been allowed to pursue the creative art of painting, perhaps his energy might have revolutionized the world through art rather than through destruction. This is simply a plea to infect our young people with the germ of creativeness, no matter what the chosen field. As adults

they will never find time nor desire to plan a wave of destruction such as we now are seeing.

There is nothing that makes for a more sincere sense of comradeship than the common search for truth. No field of endeavor, more than science, has been more effective in removing the intellectual barriers between men and women and between nations. There is an international fellowship between scientists of all nations which no war can ever annul, although it may break the lines of communication temporarily. If this scientific method were, in youth, to become a habit with everyone, then our future statesman would derive as much joy from creating the perfect international relationship as the scientists now experience in performing the perfect experiment. Through science such a system of international coöperation has already developed that it may well serve as a pattern for other fields of coöperation. The very fact that this healthy international situation has automatically sprung into being indicates the power and the value of the scientific method of thought. Not that a scientist is a superior being. In fact, he must be quite humble, for he knows how dependent everyone of his own contributions is upon the labors of thousands of scientists before him. No real scientist could ever create the idea that the German, for example, is superior to any other man. No real scientist could desire of his own free will to create a more perfect explosive or poison gas which would have the sole purpose of destroying the most interesting scientific mystery in existence—man. But he could enjoy creating a force sufficiently strong to smash an atom, for the purpose of understanding how the universe functions.

Totalitarianism and the scientific method are opposed to one another, for in the former case one should not have independent thoughts, whereas scientific method cannot exist if there is no independent thought. For the same reason democracy is compatible with the scientific method and, in return, the scientific method will help preserve democracy.

The responsibility for a better world, then, comes back to us as individuals, that is, to our way of thought. If we think as scientists who seek nothing higher than the truth and if we think as humane doctors, with faith and helpfulness toward each other, we cannot help but be good neighbors. In other words, honesty in thought and tolerance and helpfulness toward each other are the traits we should cultivate in our children by whatever means they can best be developed. This is where the majority of women can be of great help to any nation, for they as mothers and as teachers have so much to do with the development of the way of thought. That is why the Nazis take their boys away from home at a very young age in order to train them in the *Mein Kampf* evils. This, to me, is one of the chief reasons for the higher education of all women. Let us do as Pasteur says: "Take interest, I implore you, in those sacred dwellings which one designates by the expressive term Laboratories. Demand that they be multiplied, that they be adorned. These are the temples of the future—temples of well-being and happiness. There it is that humanity grows greater, stronger, better."

An extremely good illustration of the practical value of helping ourselves

by helping our neighbors can be found in the study of tuberculosis. It is true our national death rate is still decreasing (from 43.1 to 41.9 per 100,000 in the years 1942 and 1943, respectively), but Dr. Kendall Emerson, Managing Director of the National Tuberculosis Association, points out that the downward trend has slowed and may slow still more due to present conditions which lead to a decreased resistance, caused by longer hours of work, strain, anxiety, inadequate diet, broken rest, overcrowded homes and shortage of medical and nursing personnel. The report of Dr. Herman E. Hilleboe, Chief of the U. S. Public Health Service Tuberculosis Division, is very illuminating when he shows that death rates in our own cities, due to tuberculosis, vary from 15.6 to 275.5 per 100,000 and that the very high rates in certain cities can be accounted for largely on the basis of the high population percentage of Negroes, who have a recognized high susceptibility to the disease. So long as our neighbors are coughing with tuberculosis, we ourselves are not safe.

Likewise, so long as our neighbors' heads are filled with evil thoughts we cannot let our minds dwell on the higher things of life. This we are experiencing right now in a very real way.

And now to come back to the pleasant event of this afternoon, all I can say is that I sincerely appreciate all the kindnesses this afternoon, the opportunities I have had and the ones I hope still to have to try to do something helpful in science. I am deeply touched with the challenge given to me this afternoon.



## Charles Hartwell Cocke

1881-1944

On August 3, 1944 Charles Hartwell Cocke died suddenly at his home in Asheville. His death came at a time when his activities and interests were undiminished and when his great influence was extending. It brought sorrow to his many friends in and out of the profession and to innumerable patients who had known the depth of his understanding and the warmth of his sympathy.



Charles Hartwell Cocke  
1881-1944

Hartwell Cocke was born in Columbus, Mississippi, on December 1, 1881, and graduated from Cornell University Medical College in 1905. He served his internship in the Presbyterian Hospital of New York City—one of a distinguished group, many of whom became leaders in the Medicine of our time. His practice in internal medicine at Asheville and his special interest in tuberculosis brought

him in contact with physicians and patients throughout the country. He was a Fellow of the American College of Physicians, Chairman of its Board of Governors for several years and Vice-President in 1942, 1943 and 1944. He was a Past President and Secretary of the Buncombe County Medical Society and a Past Vice-President of the Medical Society of the State of North Carolina. In 1932 he served as Vice-President of the Southern Medical Association and in 1937 was chairman of its Section on Medicine. He was a Fellow and former Vice-President of the American College of Chest Physicians; a member and in 1934 a Vice-President of the American Clinical and Climatological Association. He was a member of the American Trudeau Society, the American Association of the History of Medicine, the American Sanatorium Association, the Southern Interurban Clinical Group and the National Tuberculosis Association. He was a corresponding member of the International Union against Tuberculosis. He served as Attending Physician at the Asheville Mission Hospital and the Biltmore North Carolina Hospital; as Consulting Physician at the Patton Memorial Hospital in Hendersonville. He was one of the Medical Directors and Attending Physician at Zepher Hill Sanatorium.

To all of his activities Hartwell Cocke brought penetrating intelligence, mature judgment and the light touch of humor so that membership with him on committees and boards became a memorable and pleasant experience. Above all he possessed the gift of friendship. His interest in people was unfeigned and went far beyond mere acquaintance. His desire to aid others had no limits and many a medical student and many an unfortunate patient knew his kindness and benefited from his practical helpfulness. Hartwell Cocke's brisk manner, cheerful smile, unfailing courtesy and warm sympathies will be remembered always by those who knew him. His work in the science and art of medicine, quietly and modestly performed, will live long and will serve as a fitting memorial of a wise physician.

DAVID P. BARR

## AMERICAN TRUDEAU SOCIETY

### Pacific Coast Tuberculosis Control Conference A Report of the Committee on Clinic Procedure

Dr. Herbert R. Edwards, *Chairman*

Dr. Edward Kupka  
Dr. R. Alec Brown

Dr. Herbert Mantz  
Dr. Paul S. Phelps

Dr. Paul P. McCain

Under the joint auspices of the Committee on Clinic Procedure of the American Trudeau Society and the U. S. Public Health Service, a group of 20 tuberculosis control officers from the Pacific States gathered in Sacramento, September 13 and 14, 1944, to discuss their mutual problems. Dr. H. E. Hilleboe, the Medical Director in charge of the newly created Division of Tuberculosis of the U.S.P.H.S., and his Chief Radiologist, Dr. Russell Morgan, were the guests of the conference.

Coming on the heels of the announcement that the Bulwinkle Bill had been passed by Congress and signed by the President, this meeting took on special importance, since it served as a forum on the subject of the tuberculosis program on which the Federal Government is about to embark.

The first session was devoted to a recital by each conferee of the present tuberculosis program of his jurisdiction. It was evident that a great variation existed in the practices and programs of the various jurisdictions, some being based on historic evolution, some on the availability of funds and some on the special problems to be met.

The second session was devoted to a discussion of the minimal lesion, the most common category of pulmonary tuberculosis being discovered in present-day mass surveys. Dr. Chesley Bush and Doctor Morgan presented films for discussion by the group, on which wide differences of opinion were elicited because of their border-line character.

During the third session, Doctor Hilleboe made an exhaustive presentation of the fields of tuberculosis control in which his agency is to expend money and effort.

The fourth session was devoted to recent developments in radiology as applicable to tuberculosis. Doctor Morgan reviewed the principles underlying the technique of chest X-ray films and described the photoelectric timer.

The material presented at this conference was of the most practical value. The conference served to acquaint each control officer with what his neighbors are doing and allowed for exchange of information between the Federal division and the men doing the work in the states, counties and cities of the Pacific Coast area.

## ANNOUNCEMENT

### Baruch Committee on Physical Medicine

The Administrative Board of the Baruch Committee on Physical Medicine has announced the granting of an additional total sum of \$185,000, which is being given by Mr. Bernard M. Baruch for the further advancement of the program in physical medicine and the physical rehabilitation of those disabled in the war. This sum has been divided into seven grants as follows: \$50,000 to the Massachusetts Institute of Technology, Cambridge, Massachusetts; \$40,000 to the Medical School of the University of Minnesota, Minneapolis, Minnesota; \$30,000 to the Medical School of Harvard University, Boston, Massachusetts; \$30,000 to the Medical School of the University of Southern California, Los Angeles, California; \$15,000 to the Medical School of the University of Iowa, Iowa City, Iowa; \$15,000 to the Medical School of the University of Illinois, Chicago, Illinois; \$5,000 to Marquette University Medical School, Milwaukee, Wisconsin.

The grants to Massachusetts Institute of Technology and the University of Minnesota are in addition to the gift of \$1,100,000 made by Mr. Baruch in April of 1944, at which time grants were made to Columbia University College of Physicians and Surgeons, New York University College of Medicine, the Medical College of Virginia and for minor research and fellowship programs for the advancement of physical medicine.

The present gift to Massachusetts Institute of Technology is in support of a five-year program of training and research in electronics, instrumentation and physics in relation to medicine, to be carried on under the auspices of the Department of Biology and Biological Engineering. It was the conviction of the Scientific Advisory Committee of the Baruch Committee on Physical Medicine that Baruch Fellows and other physicians should have more than a superficial knowledge of the physics and technology underlying the physical methods and instrumentation used in this field and it was suggested that training in this aspect might effectively be centred at the Massachusetts Institute of Technology. The program will be under the general supervision of Doctor Francis O. Schmitt, head of the department of biology and biological engineering and under immediate supervision of Doctor K. S. Lion, assistant professor of applied biophysics, who is an expert in physical instrumentation.

The grant of \$40,000 to the University of Minnesota is to support the development of a three-year teaching and fellowship program in physical medicine. The primary objective of the program is to be the furtherance of fundamental training of research workers and teachers. The program has as its basis the development of scientists in the field of physical medicine. As an auxiliary to this basic training will be developed facilities for the training of clinicians and technicians.

The other grants have been allocated from the fund of \$200,000 given by Mr. Baruch in April. The sum of \$30,000 was granted to Harvard University

Medical School for establishment of a three-year program to provide fellowships or residencies to be used for the benefit of qualified physicians who are selected to be trained in this field. This sum will be administered by a strong standing committee on physical medicine recently appointed by Dean C. Sidney Burwell of the Harvard Medical School, composed of Doctor J. B. Ayer, Doctor D. Denny-Brown, Doctor W. T. Green, Doctor J. H. Means, Doctor A. L. Watkins and Doctor E. M. Landis (Chairman). Appointments to the fellowships, which generally carry stipends of \$2500, will be made annually but may be renewed to provide up to three years of specialized study and research. Emphasis will be placed upon training a few men in basic research and clinical investigation.

Unusual opportunities for clinical experience and research in the psychologic and psychiatric aspects of physical medicine will be available at Harvard. The first year will be wholly or in part devoted to basic research related to physical medicine in one of the pre-clinical sciences such as physiology, anatomy or biophysics. The second year will be spent in clinical training in physical medicine at the Massachusetts General Hospital and other hospitals affiliated with the Harvard Medical School. In the third year, fellows will be assistants in physical medicine with clinical responsibilities. For candidates with extensive previous training, one-year clinical fellowships will also be granted. Applicants must have an M.D. degree from an approved medical school and a minimum of one year of internship in an approved hospital. Applications may be obtained from the Dean, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts.

The sum of \$30,000 is granted to the University of Southern California to inaugurate a program of teaching and research in physical medicine in its Medical School. The sum of \$15,000 is granted to the University of Illinois to inaugurate a teaching program in physical medicine at its Medical School. The sum of \$15,000 is granted to the Medical School of the University of Iowa to assist in a joint research and teaching program concerning the effectiveness of different methods of applying heat to the deep tissues of the human body. Finally, the sum of \$5,000 is granted to the Medical School of Marquette University, Milwaukee, Wisconsin, for continuance of research in the physiology and pathology of nerves and muscles as related to physical medicine.

In discussing these grants Doctor Frank H. Krusen, the director of the Baruch Committee, pointed out that Mr. Baruch had been particularly interested in the important field of electronics as applied to medicine and he said that the centre at Massachusetts Institute of Technology gave promise of revolutionizing the application of electronics in the diagnosis and treatment of the sick. Doctor Krusen expressed gratitude concerning the establishment of fellowships in physical medicine at Harvard and mentioned the advantage to the field of physical medicine in having this great centre assume leadership in the training of fellows. He also stated that the aid given to the University of Minnesota and the University of Southern California would extend the activities of the Baruch Committee into the midwest and far west and thus tend to strengthen this important program. In conclusion, Doctor Krusen announced that the

Administrative Board does not contemplate the recommendation of any further large grants for the establishment of additional departments of physical medicine in our medical schools. He said that the Baruch Committee would now turn its main attention toward the adequate development of the centres already established, toward providing advice in the organization of proper teaching of physical medicine in medical schools and, through its strong Committee on War and Postwar Physical Rehabilitation and Reconditioning, would attempt to promote proper development of physical medicine in the rehabilitation and reconditioning of both military and civilian casualties of war. The Board agreed that Mr. Baruch's gifts had served as a means of providing prompt coördination of the entire program for rehabilitation of our wounded and for the provision of the trained personnel so greatly needed in activating this program.

### NOTICE

Prof. Dr. Fernando D. Gómez, Director, announces that the third post-graduate course, Diagnosis of Pulmonary Tuberculosis, will be given in the Instituto de Tisiologia "Prof. Juan B. Morelli," Montevideo, Uruguay, March 5 to 17, 1945.

# ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS<sup>1,2,3</sup>

## XIII. Incidental Findings of Isolated Tuberculous Foci in the Lungs Apart from the Primary Complex

### ("Focal Extension")

KORNEL TERPLAN

It might have been expected that in the course of a systematic postmortem study on the incidence and pathogenesis of tuberculous lesions in children and adults a variety of observations should be made which differ from the well known findings of a closed primary complex and from the typical pictures of acute progressive primary tuberculosis or of chronic pulmonary tuberculosis. We have pointed out in one of the foregoing papers (1) that localized incidental findings of tuberculous lesions in cases in which the cause of death was not tuberculosis might prove more advantageous for the study of pathogenesis than extensive lesions of tuberculosis, especially of the chronic types. In the course of these studies, however, it became more and more obvious that only by attempting to solve relatively restricted problems in such cases with incidental lesions of tuberculosis could we ever hope for some success—limited as it might be—in approaching the problem of pathogenesis in the much more complicated and extensive anatomical lesions as found in chronic tuberculosis, especially in the adult.

This paper will deal for the most part with such incidental findings of one or more focal lesions in the lungs, which were observed in addition to a typical primary complex in various phases of regression, including the firmly calcified or ossified state. The genetic relationship of these few or even single lesions to the primary focus was of foremost interest. At the very beginning of these studies, more than eleven years ago, we were impressed by occasional findings of one or more, usually small, focal lesions, showing complete identity in their structure with the primary focus, which, in the majority of these observations, could be identified by its relation to the tuberculous lymph nodes forming the Ranke complex. These findings were the more surprising, as they seemed to

<sup>1</sup> From the Department of Pathology, Medical School, University of Buffalo, and the Pathology Laboratories of the General Hospital and Children's Hospital, Buffalo, New York.

<sup>2</sup> The three papers contained in this issue, and a series of papers to follow, are a continuation of our anatomical studies on human tuberculosis, the first part of which was published in the Supplement to the AMERICAN REVIEW OF TUBERCULOSIS, August, 1940, volume 42. Again, these studies have been greatly aided by generous grants from the Junior Board of the Buffalo General Hospital.

<sup>3</sup> The technical histological work was done by Miss Helen Sanderson, the charts and microphotographs by Medical Illustrator, Melford Diedrick. The roentgenograms were prepared by Doctor Koenig and his associates in the X-ray Department of the Buffalo General Hospital; the secretarial work was done by Miss Norma Wilkins. My associate, Dr. Charles F. Becker, has given valuable help in the arrangement of the material for publication. To all, I wish to express my appreciation and gratitude. [Kornel Terplan]



disprove the belief held by some investigators at that time, that there is usually a structural distinction between the true primary focus and foci of postprimary nature. In some of our cases, still at the beginning of our study, such additional foci—in the presence of a typical complex—were found in apical location. In most of these latter observations there seemed to be no evidence of hematogenous dissemination from the primary complex. Later on, as an increasing number of reinfection complexes were analyzed, it was found that in these cases, too, occasionally one or more lesions were present outside of the area of the healed or of the more recent focus (of reinfection), showing the similar structure and but little—if any—difference in size with either the old true primary focus or with the more recent focus belonging to the reinfection complex.

In analyzing the genetic relationships of these additional foci to the primary focus the following possibilities had to be considered: (a) simultaneous infection from without, with formation of more than one primary focus; (b) a true superinfection in the early phase of the first infection; (c) focal extension, either by direct intracanalicular spread through the bronchi to other areas—the primary focus being the source for this extension—or by hematogenous metastasis from the components of the active primary complex. This latter type we prefer to call “focal hematogenous extension” in contradistinction to the multiple and usually small (miliary) hematogenous tubercles. In evaluating these routes of spread from the primary focus we can be guided somewhat by carefully analyzed macroscopic and microscopic findings, including detailed dissection. As actual observation of the formation of these postprimary lesions is naturally impossible in our anatomical material, we have to be content in the discussion of these matters with pointing to the more unlikely ways of spread rather than in proving a specific one. Only in a few instances in which such focal findings appeared of fairly recent nature in the presence of a recent complex, their close interdependence seemed obvious. In the majority of the cases included in this paper we have found these additional foci in a relatively late state of regression. The fact that to no one of them a tributary complex was found made it probable that they were not “primary” foci in the strict sense. It is essential to be fully conscious of the great restrictions imposed upon the pathogenetic analysis of histological pictures by the apparent uniformity of the tissue reactions to tuberculous infection, especially if there is little difference in the size of the foci formed.

We now shall discuss the possibilities mentioned above as to the source of infection leading to the formation of such additional foci. A simultaneous infection taking place at the same time at which the primary complex is formed is most improbable. It would be difficult to understand why no spread to the regional lymph nodes should occur from one or more of these additional foci. In spite of exceptions to the law of Parrot, which we have reported in some of the foregoing papers (III (2) and XII (3)), the evidence that first infection produces the classical picture of a primary complex is so clear in the majority of our observations that it, alone, can be used—at the present time—as a basis for any pathogenetic analysis of tuberculous lesions. Although the hematogenous

route in many cases of progressive tuberculosis in children is directly or indirectly the most important way leading to dissemination of tubercle bacilli in different organs, it will be shown from our observations that this route is a very unlikely one for establishing the few large focal lesions under discussion. With certain exceptions, and these will be cited later, in most of our observations there is no anatomical evidence of hematogenous seeding. If, however, a few obviously hematogenous tubercles were found, especially in the lungs, which in the presence of an active complex might be expected, they differed markedly from such focal lesions which, as stated above, showed all the gross and histological criteria of the primary focus. They were small and—as seen in case 5004—of more recent state. In all these latter cases a few tubercles were also found in organs outside of the lungs, such as the spleen, liver or kidneys, which could only be reached by the hematogenous route. On the other hand, in all such cases in which, postmortem, the typical picture of progressive primary tuberculosis with generalized miliary seeding was revealed (as in case 1 of the children's group) the hematogenous way might be responsible also for the formation of large single foci apart from the area of the primary complex, although their gross appearance in the presence of numerous miliary tubercles might suggest a different pathogenesis.

In the majority of our observations, however, it seems much more likely that other ways might better explain the findings of these additional foci. They could result either from superinfections or they could be caused by direct spread of tubercle bacilli from the primary focus in its early active state before encapsulation has taken place. This latter type of spread, leading, as a rule, to but few additional lesions not greatly varying in size and structure from the primary focus, we wish to call "focal extension." We have to admit that superinfection can occur, even in very early phases of first infection. The source for tuberculous infection is frequently a permanent one in close contact with the harbinger of the primary lesion. If this conception is correct, such a superinfection has acted on the lung tissue already definitely changed by the still recent first infection. This change alone can explain the lack of further lymphogenous progression which, in striking difference to the primary complex, is absent, at least in a macroscopic sense.

In one of the preceding papers (II (4)) on the types of primary tuberculosis in children, the various ways of extension and progression were amply discussed in all the active cases in which tuberculosis was the cause of death. The importance of intrabronchial spread was stressed in those groups in which, either by direct communication of the disintegrating primary focus with the draining bronchus or by massive rupture of a caseated hilar lymph node into the lumen of a bronchus, rapid progression by aspiration to different parts of the lung could be demonstrated. In our series the histological analysis of several active primary foci, in relatively early phases of their establishment, shows that there is distinct perifocal extension, involving contiguously adjacent acini, even if at gross inspection this focus appeared already well encapsulated. In such early phases, during the formation of the primary focus, it is most likely that additional acini

are affected by contiguous involvement of or by aspiration into adjacent bronchioles. The size of this very first pneumonic lesion, possibly dependent to some extent on the intensity of infection, might determine the gradual involvement of adjacent bronchioli and smaller bronchi.

There is, however, a second possibility leading to this focal spread, not necessarily restricted to the side of the primary focus, and this is through infiltration of the wall of the bronchus, from an actively caseated, closely attached lymph node. As will be shown later, such a microscopic infiltration can be present without a grossly recognizable erosion in or perforation of the bronchial tube. It is possible that tubercle bacilli might be excreted through the mucous glands in the bronchial wall, at the site of recent tubercles, without actual massive perforation. Gross perforation can play an important rôle in rapid intra-bronchial progression of tuberculosis as well as it can lead to relatively mild localized endobronchial tuberculosis, with obturation atelectasis without serious sequelae. In all cases included in this paper, except case 2 (C. H. 539), we were not able to demonstrate any evidence of recent or old extension of the tuberculous process from the hilar lymph node into or through the wall of the bronchus. In spite of this, relatively mild and actually only microscopic perforations should be ruled out as sources for focal extension only if actually proved by histological analysis.

That conditions for focal extension are probably favorable in the early phase of the primary focus is proved by the very few cases known from the literature in which these early lesions were incidentally found. In these, the exudate is not as yet caseated, but rather highly cellular. Only complete, firm caseation and more or less complete encapsulation will prevent aspiration by the draining bronchus. On the other hand, cavitation in primary foci naturally opens broad channels for rapid progression. Ghon and his collaborators have shown that already, in these very early phases in which the pneumonic area is literally swarming with tubercle bacilli, there is distinct microscopic evidence of lymphogenous spread of the infection to the nearby regional lymph nodes. It does not seem improbable that, in addition, tubercle bacilli could also be aspirated from the primary foci in their relatively young evolutionary phases to form new focal lesions by canalicular spread.

In several of the preceding papers attention was called to these focal lesions apart from the primary complex. In one case of progressive primary tuberculosis in children, with typical lympho-hematogenous dissemination originating from the primary complex, one single focus of the same appearance as the primary focus was found in the opposite lobe (case 22, paper II). In another case (no. 23, the same paper), several foci in the area of the primary focus were present, in combination with localized intrabronchial spread in the same lobe, leading to restricted atelectasis. In paper III on primary multiple foci without lymph node changes, this question of focal extension again had to be considered; one of these foci represented a pencil-like, chalky-calcified lesion which apparently had formed in the lumen of a small order bronchus. In paper VII (5) on reinfection complexes, in 2 cases similar observations were made. In

one of them, case 2, several foci forming the cores of the primary complex and of the reinfection complex were arranged within a rather close radius. Their interrelationship seemed obvious and it was impossible to point to the real primary focus in these groups. In another observation (case 10), a few smaller tubercles were found in the right lung which apparently had extended from the reinfection focus in the left lung. This reinfection focus showed a very clear peribronchial arrangement of the entire caseated area. There were no hematogenous tubercles. In discussing briefly these findings, especially those seen in the active cases of 2 children, it was stated: "As the lymph nodes draining the areas of these additional foci, especially if found in other lobes or in the opposite lung far apart from the Ghon focus, are entirely negative, we cannot consider these additional foci as simultaneous effects of the same primary infection, in spite of the fact that their histologic structure might not differ from that of the primary focus. This applies especially to their less active states, and even more so to the older phases of advanced organization, including calcification." It was stated there that "although localized superinfection cannot be ruled out (on theoretical grounds), our material seems to support the view that this 'focal extension' from the primary lesions in its active phase, producing one or more additional foci of similar size and structure like that of the Ghon focus, does occur not only within the area close to the primary focus but also in more distant parts of the lungs, including the subapical fields."

It will be shown from our material that only in very few cases presenting relatively early phases of extension from the primary focus, before calcification takes place, a pathogenetic analysis can be attempted. Only in these, the gradual aging of the focal structures has not obscured their probable original interdependence.

How far this type of additional infections, be it from real focal extension or from superinfection, might lead to more extensive tuberculous involvement, especially in the subapical and apical areas, is impossible to state from the relatively small number of our incidental findings with recent focal lesions. However, from a few postmortem findings which form the substrate for the forthcoming paper (no. XIV), it is evident that localized subapical tuberculosis can develop in direct connection with a primary focus. That the subapical fields are a preferred site for the primary focus had already been pointed out by Ghon in his monograph on the primary pulmonary focus in tuberculosis of children. In our few cases, which will be discussed in detail in the forthcoming paper, there was localized progression of the tuberculous process around the primary focus with the picture of fairly limited intrabronchial extension. Lymphogenous progression included for the most part one or two regional lymph node groups.

We have found only few observations in the literature dealing, at least in part, with such additional tuberculous focal lesions in the presence of an active complex. Ghon and Kudlich (6), in discussing a case in which 17 primary foci-like lesions were found in a three and one-half year old girl, stated that there are two possibilities to explain this large number of primary foci, which in their

case varied between pinhead and cherry-pit size: Either each one was actually a primary focus or a large part of them had developed in a secondary manner following aspiration from the true first infection. According to Ghon, it is rather difficult to decide whether in these cases a true superinfection has occurred or whether a focal lesion of nearly the same size as the primary focus is actually a metastasis from intrabronchial aspiration. In a paper about the portals of entry of tuberculosis by Ghon and Kudlich (7), these difficulties are plainly presented, together with charts and photographs showing such additional foci of primary focus character. In one of these there was even minimal lymphogenous progression from the second focus, while the obviously true primary focus had produced a very massive complex restricted to its own side. In discussing the possibility of true superinfections, Ghon felt that it is not known at what time after the primary infection the so-called "allergic change" (*Umstimmung*) is established, preventing a second (exogenous) infection.

Since anatomists observe only the results of such infections, especially if found in the less recent states, it is frequently impossible to determine their time relation to the real first infection.

According to Schuermann (8), tuberculous foci which developed at a time close to that of the primary focus might show considerable involvement of the regional lymphatic channels. He also states that foci of superinfection or metastatic foci are much slower to be impregnated with calcium, and calcification and bone formation is less marked or not at all present. With this we cannot agree, as the results of the detailed anatomical studies published in this paper will show. Schuermann has seen cholesterol crystals especially in hematogenous metastases, surrounded by thick fibrous capsules. In spite of this, however, he admits that the structural character of a lesion does not allow any specific decision as to its pathogenesis.

Kuess (9) found that there usually is only one primary focus, but sometimes, close to this, a second focus along the nearest bronchus or in the subpleural area can be found. In a small number of cases in the material of Kuess, the primary focus consisted of a group of densely arranged smaller tubercles; rarely, there were multiple foci in different parts of the lung, and Kuess found it obviously difficult to decide whether some of these were not secondary foci. A similar view was held by Puhl (10), according to whom multiple focal lesions are either caused by a simultaneous infection or by a "reinfection" from the real primary focus, following rather closely its formation. Pagel (11), on the other hand, appears skeptical as to the simultaneous establishment of multiple primary foci. Most of them, he feels, are hematogenous metastases or superinfections. Blumenberg (12), too, has seen primary multiple foci in 4 cases; they were in the same lobe in all 4.

Whether or not Huebschmann (13), in his monograph on the pathological anatomy of tuberculosis, is referring to these focal lesions, we cannot state with certainty. All that was seen of recent single lesions outside of the primary complex by Huebschmann was, without exception, 1 to 2 cm. below the apex. Although these "small" lesions were thought to present hematogenous metastases of the primary complex, Huebschmann admitted that they could also

result from a low-grade (*unterschwellig*) exogenous reinfection (meaning "super-infection"), the primary complex being not as yet healed. Wurm (14), Pusik and Strukow (15), and Lincoln (16), too, favor the hematogenous metastatic nature of the isolated apical lesions known in the literature as Simon's foci, although Pusik and Strukow admit that they might also form from lymphogenous and contiguous spread. But we learn only from Wurm's histological analysis that these so-called Simon's foci have a structure similar to the primary focus—including the marked tendency to calcification—while Pusik and Strukow found in the capsules of these apical lesions the structural type of both the primary and the reinfection focus. Lincoln's comment on these apical foci is based on roentgenological observation rather than on anatomical analysis. According to her, these lesions vary from miliary to large irregular masses. Occasionally she found it difficult to distinguish a large apical lesion from the primary focus, but, she adds, the apical lesion usually calcifies more quickly than the primary focus and is not accompanied by enlargement of the regional lymph nodes. Huebschmann's and Lincoln's descriptions apparently refer to a variety of postprimary lesions, including clusters of apical miliary tubercles as well as isolated single focal lesions. Such is also our impression from other discussions of Simon's foci, including those by Wurm, and Pusik and Strukow, mentioned above.

Loeschke (17) observed foci in children in cases in which the primary focus was in communication with the bronchus. Usually there were also single foci in proximity to the primary focus. He found, in addition, that scars arising from cheesy, pneumonic aspiration foci are very similar to those of the primary focus.

Frimann-Dahl and Waaler (18), in their material of 200 consecutive post-mortem examinations used for roentgenological and pathological-anatomical studies of the primary complex, report 7 cases with two primary foci, to only one of which a regional lymph node was found. Both of these foci were macroscopically and microscopically similar. In discussing this finding it is felt by these two authors that the focus without the complex was formed later than the true primary focus. The histological reaction in the lung tissue is the same, but it is claimed that "the lymph channels are already closed off just as in the secondary state." One case with four, and another with five foci are mentioned, and among these it is claimed that actually only one focus was primary. Their brief discussion of this phenomenon is closed with a statement that cases with foci of the same structure as the primary focus, which are, however, in reality secondary foci, are not a rarity.

The material examined for this study includes the anatomical findings in 6 children and 49 adults.

#### CASE REPORTS

*Case 1:* (B.G.H. 3653) Fourteen year old white boy. (Plate 1)<sup>4</sup>

*Macroscopic report* (only findings pertaining to tuberculosis will be listed): About a pea-sized, firm, cheesy tuberculous focus was found in the middle third of the left lower lobe

<sup>4</sup> The microphotographs are, in general, low magnifications (about 7×). They are consistent in each case unless otherwise indicated.

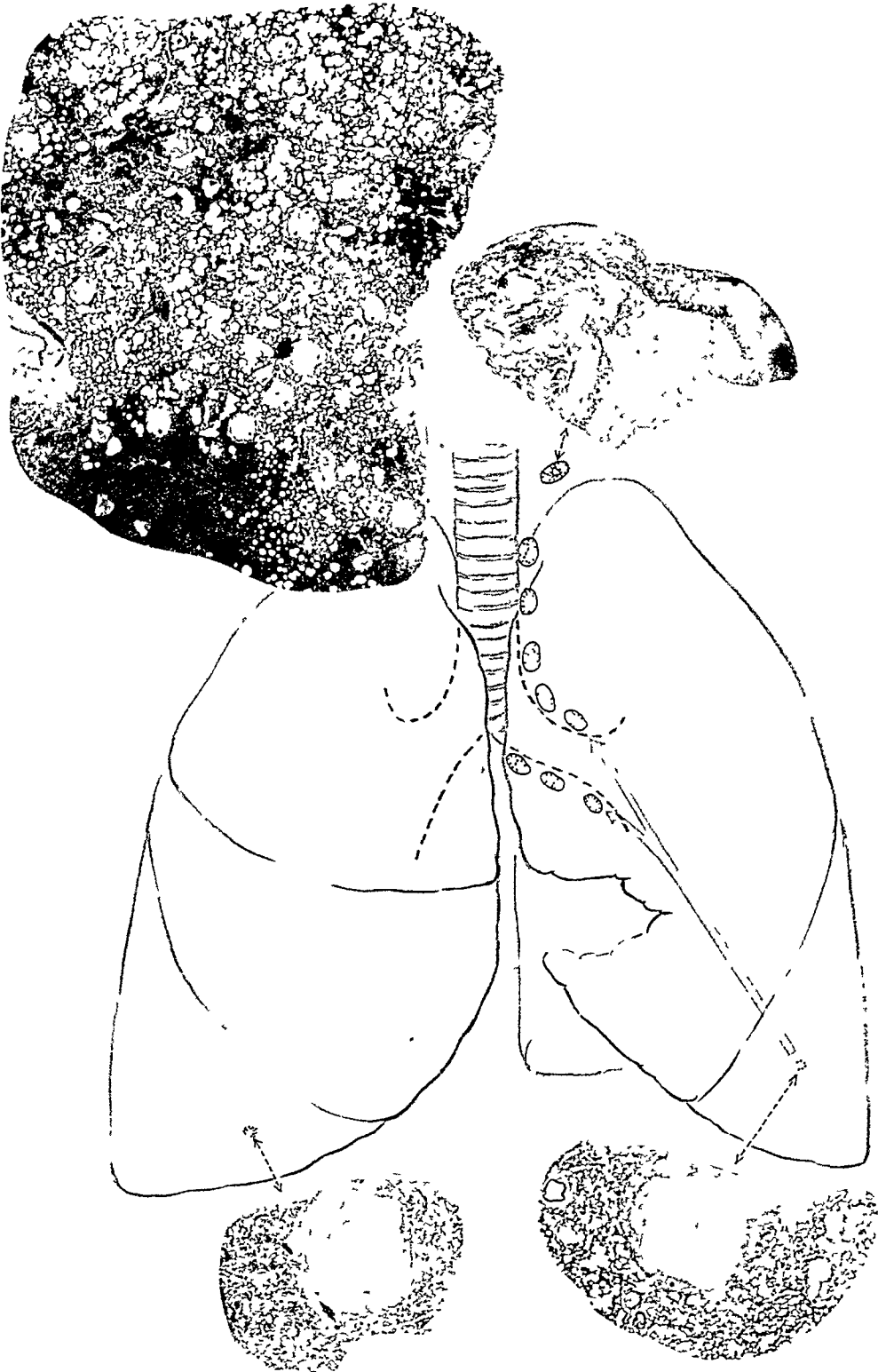


PLATE 1

and extensive caseation of all regional lymph nodes, including the bronchopulmonary and lower and upper tracheobronchial group on the left side. Distinct tuberculous hyperplasia was seen with only minimal caseation of the left paratracheal group, and complete caseation of a bean-sized lymph node in the left venous angle, with central cavity formation. A second pea-sized, firm, cheesy focus was found in subpleural position near the base of the right lower lobe at the posterior surface. In all lymph nodes draining the right lung no gross tuberculous changes were seen. In both lungs innumerable miliary tubercles were present, measuring less than 1 mm. in diameter. There were many minute miliary tubercles in the liver and spleen, with lentil-sized tuberculous plaques in the capsule of both organs and with tuberculous perihepatitis and perisplenitis; many tuberculous infiltrates and miliary tubercles in both kidneys; caseated tubercles in the left seminal vesicle; a few recent tuberculous ulcers in the lower ileum and in the cecum, along with scattered miliary tubercles in the mucosa and recent tuberculous hyperplasia in one lower mesenteric lymph node without caseation. This picture of overwhelming hematogenous tuberculosis was completed by several hemp-seed sized caseated tubercles in different parts of the brain, including gray and white matter of the cerebellum, with two small tubercles in the ependyma above both caudated nuclei, combined with the typical picture of tuberculous meningitis with jelly-like exudate, apparently occluding the foramina and the basis of the brain.

There was hardly any difference in the volume of the primary focus and of the second single focus in the lower lobe of the opposite lung. The diameter was about 4 mm. in both. Grossly they both had a firm, caseated consistency, pointing to early fibrous encapsulation.

In the histological picture the caseation of the primary focus is apparently more complete. The encapsulation of both foci appears very distinct in connective tissue and elastic tissue stains. This latter stain, however, shows the elastic pattern of the alveolar structure decidedly better preserved in the (secondary) focus in the right lower lobe than in the primary focus. One interesting feature is localized hemorrhages along part of the circumference of the primary focus. There is but one satellite tubercle very closely attached to the capsule of the primary focus, while in intimate contact with the capsule of the secondary focus there is active tuberculous granulation tissue with many Langhans' giant cells and epithelioid cells, along with the typical proliferation of fibroblasts directed against the large caseated core. Tubercle bacilli stain shows the presence of a fair number of in part well preserved, in part fragmented and granular tubercle bacilli in different areas of the focus from the right lower lobe. In several sections cut through different levels of the primary focus no acid-fast bacilli are found in spite of the fact that in addition to compact caseation very much nuclear debris is strewn over the entire field. In the surrounding tissue are scattered miliary tubercles consisting mostly of epithelioid and giant cells, here and there with slight central necrosis. In analyzing the areas which grossly appear to be studded with miliary tubercles, it is clear that some of these already involved smaller bronchi, filling out part of their lumen with proliferating epithelioid and giant cells. Other smaller bronchi appear filled out with recent epithelioid giant cell tubercles, with most of their epithelial lining intact.

The picture proves that we are obviously dealing with a combination of hematogenous miliary seeding with early intrabronchial spread. Whether this is dependent on the progressive growth of primarily hematogenous tubercles or on aspiration from the large secondary focus in the right lower lobe could hardly be decided. The lymph nodes draining the right lung were histologically not examined. On very close inspection of the entire lymph node chain draining the right lung there were no grossly visible tubercles.



The histological picture of the lymph nodes regional to the primary focus shows a fairly completely caseated area with central disintegration, surrounded by numerous noncaseated epithelioid giant cell tubercles. In sections through the lymph nodes and the attached bronchus leading to the left lower lobe, no tuberculosis is found in its wall. In several lymph nodes there is actual cavitation in the centre, and this is especially marked in sections from the lymph node of the left venous angle. The cavitation here is more pronounced than in the more proximal lymph nodes close to the primary focus.

*Note:* The X-ray picture of the undissected lung is very typical of dense hematogenous miliary tuberculosis. There is no calcification present; only a minute speck above the left major bronchus points to a calcified structure, which proved to be a phlebolith in the *ductus Botalli*.

Location and size of both the primary and the additional huge postprimary focus are shown together with the caseated angulus lymph node regional to the primary focus and with a typical section of miliary tuberculosis in the lung tissue on plate 1.

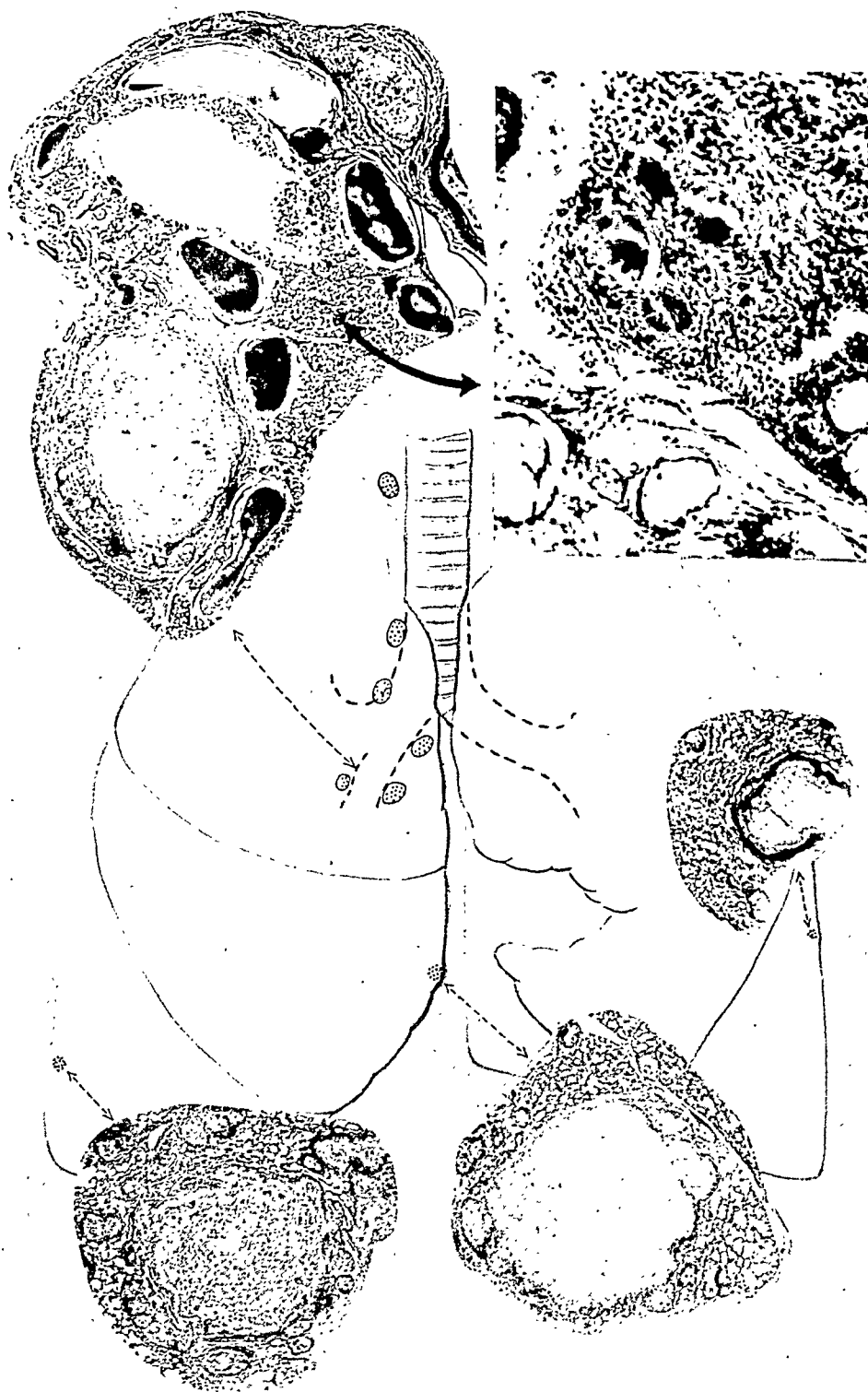
*Epicrisis:* In a case of typical progressive miliary tuberculosis, the finding of a large, single and distinctly postprimary tubercle of the same size as the primary focus is the more unusual, as all other tubercles throughout all lobes are of typical small miliary size, as seen in fairly rapidly progressing cases of overwhelming hematogenous seeding, especially in children. Whether it represents the oldest focal hematogenous metastasis within the lung or the result of intrabronchial aspiration from the primary focus in its earlier evolutionary phase can hardly be decided. Focal hematogenous spread to a single area within the right lower lobe might have preceded the event of massive miliary seeding throughout all lobes in this case.

*Case 2:* (C.H. 539) Nine month old white boy. (Plate 2)

A primary caseated focus, well encapsulated, was present in the lateral portion of the right lower lobe, in subpleural position. There was diffuse caseation of all regional lymph nodes, including those between right lower and upper lobe, the bronchopulmonary, upper and lower tracheobronchial groups, and the lymph nodes in the right venous angle. A hazelnut-sized, nodular structure very closely attached to the right pulmonary ligament, but still in loose connection with the lung tissue, was thought to be a caseated lymph node. In addition, a second, flat, firm, caseated focus was found in the subpleural area of the left lower lobe, in its middle third on the lateral surface. In all lobes there were a few scattered small, soft miliary tubercles.

In addition, there were tuberculous meningitis, with many minute tubercles in the leptomeninges, on base and convexity, and a few tubercles in the choroid plexus and the tela of the third ventricle, scattered tubercles in the liver and very few tubercles in the spleen.

The histological analysis revealed that the structure found close to the pulmonary ligament is actually another primary focus. It is of the same size and surrounded by a large number of satellite tubercles, just like the primary focus in the parenchyma of the right lower lobe. While both these foci are about 4 to 5 mm. in diameter, the additional focus found in the left lower lobe is distinctly smaller, measuring about two-thirds of the diameter of the primary focus. There is an unusual abundance of satellite tubercles around both foci in the right lower lobe (see plate 2). It is clear that many of these smaller tubercles extend into surrounding bronchi, some of which appear collapsed. But especially the lymph vessels surrounding the nearby pulmonary artery are entirely obscured by large epithelioid giant cell tubercles.



The focus in the opposite lung shows diffuse caseation and is surrounded by a wall of epithelioid cells, with a few giant cells closely encroaching upon a nearby bronchus which appears collapsed. A few minute miliary and small conglomerate tubercles are found in different sections taken from the lung. In this case there is hardly any difference seen in the elastic tissue stain between the two foci. In both, the alveolar pattern is fairly well preserved.

A section through the lymph nodes surrounding the bronchus to the right lung, especially near the right upper tracheobronchial group, reveals no appreciable narrowing of its lumen, in spite of the fact that both attached lymph nodes are almost completely caseated. There are, however, recent epithelioid cell tubercles with several Langhans' giant cells within the mucosa in the mucous glands between the cartilaginous plates. These appear of fairly recent age. In several sections examined no erosion of the mucosal lining by tuberculosis is seen. There is also evidence of localized tuberculosis within the somewhat anthracotic perihilar parenchyma, apparently in close connection with the extensive lymph node tuberculosis.

The final histological analysis proved that we actually are dealing with two primary foci of the same size and histological structure, both in the right lower lobe—one in its most lateral portion, the other within the opposite mediastinal surface attached to the pulmonary ligament. It is also obvious that some of the large satellite tubercles established around the lateral primary focus are in open communication with small bronchi. In addition, apparently direct extension from the massively caseated lymph nodes into the wall of one of the major bronchi could be demonstrated. Several tubercles were found within the mucous glands and one of them already in mucosal position just underneath the surface epithelium. This case shows further distinct evidence of hematogenous spread with several typical miliary tubercles scattered throughout both lungs. Outside of the active primary focus (or foci) there was added opportunity for intrabronchial spread from direct extension of the tuberculous process in the caseated hilar lymph nodes through the bronchial wall, involving mucous glands and mucosal lining. Careful gross examination failed to reveal evidence of any erosion or ulceration. The secondary focus in the left lower lobe, though distinctly smaller than both primary foci, has a typical pneumonic caseated structure as seen in any recent primary focus. It is, however, again much larger than the few miliary tubercles scattered through all lobes and of firmly caseated character. Grossly, it has the appearance of another primary focus, except for the absence of the Ranke complex on this side. Considering the probable pathogenesis of this large single tubercle in the left lung, we feel that gross and histological analysis of all anatomical findings seem to point to focal extension by the intrabronchial route rather than to a single hematogenous metastasis. Several sources for such an intrabronchial spread were present: the primary focus or foci, their caseated satellite bronchiolar tubercles and the tuberculous mucosa of the major bronchus contiguous to the massively caseated hilar lymph node. Especially through the latter, bacilli might have been excreted within the secretion of the mucous glands. On the other hand, in the presence of a progressive caseated primary complex with recent miliary tubercles in lungs, liver and spleen, it must be admitted that this focal extension to a restricted area of the left lung might also have been a hematogenous, though single event preceding for some time the establishment of scattered miliary tubercles.

Plate 2 shows the primary complex with the two caseated foci in the right lung surrounded by miliary satellite tubercles encroaching upon smaller bronchi; a cross section of the right major bronchus in the hilar area with the closely attached bronchopulmonary

lymph nodes in a massively caseated state. Note also one recent tubercle within the mucous glands of the bronchial mucosa and (to the right) a higher power view of this mucosal tubercle; in the left lung the additional caseated focus and a few recent miliary tubercles close-by.

*Case 3: (C.H. 157)* White female, two years, four months old.

This case has already been discussed in a previous paper dealing with bronchial obstruction in pulmonary tuberculosis in children and its relation to epituberculosis. There were altogether five about pea-sized, caseated or cheesy-chalky foci in the left upper and left lower lobe in an area close to the interlobar surface. These foci varied only slightly in their size, which was between 3 and 4 to 5 mm. in diameter. The chalky changes were more marked in two, while in three others this was found only in the central parts. They all were well encapsulated; only one of them, an obviously more recent focus, showed a large satellite tubercle. As mentioned in the previous paper, the intrabronchial extension in this case could be demonstrated by substantial caseated tubercles filling out large bronchi draining the mediastinal area of the left upper lobe. The lymph nodes regional to the left upper and lower lobes showed extensive caseation; apparently the infection had crossed to the right upper tracheobronchial lymph nodes and the lymph node in the right venous angle. Here central chalky changes were already seen, while the lymph node in the left venous angle contained a few hyaline and epithelioid cell tubercles.

A few miliary tubercles in the liver and kidney, along with the typical findings of tuberculous meningitis, concluded the picture of hematogenous spread from the pulmonary foci. There were no hematogenous tubercles in the lungs. In this case the anatomical picture itself, showing localized atelectasis, caused by obstruction of a few bronchi in the left upper lobe, pointed to intrabronchial spread of the tuberculous process from the primary focus. Extension of the lymph node tuberculosis into the lumen of the bronchus was not demonstrable in this case, but cross sections from only one bronchial level were examined. The five foci were obviously not of the same age, as two of them showed more marked chalky changes, while two others appeared firmly caseated with but minimal central deposition of chalky material.

*Case 4: (C.H. 476)* Eleven year old white boy. Cause of death: acute poliomyelitis.

In this case the findings of tuberculosis were entirely incidental. In the upper medial part of the right upper lobe there was a small pea-sized, caseated focus. There was complete caseation of the upper tracheobronchial lymph nodes and bronchopulmonary lymph nodes draining this area. The only additional tuberculous lesion found in the lungs was a pinhead-sized, firm, subpleural tubercle with central chalky changes, in the lateral angle of the left lower lobe near the base. All the lymph nodes draining the left lung did not contain any tuberculous foci. The primary focus was, microscopically, well encapsulated by a hyaline band and showed central chalky changes and one epithelioid giant cell tubercle in close connection with the slightly irregular hyaline band. The histological picture of the smaller focus in the left lower lobe was essentially the same. Here, too, only one epithelioid giant cell tubercle was found within the periphery of the fibrous capsule. It seemed as if the hyaline organization was even more pronounced than in the primary focus, possibly because this focus was distinctly smaller. Only one lymph node from the upper tracheobronchial group on the right side was examined. It showed massive, diffuse caseation with early chalky changes in the centre. In this case there was no evidence of any hematogenous spread in spite of the quite extensive complex changes in the lymph nodes draining the primary focus.

*Case 5: (C.H. 785) Nine year old boy. Cause of death: Still's disease. (Plate 3)*

Outside of the typical changes of chronic deforming arthritis, with severe anemia and ascites, the following findings of tuberculous nature were present. In the right lower and middle lobe: several chalky and partly calcified foci varying in size from a large pea to a small lentil, with extensive chalky, caseated changes with some calcification in the interlobar bronchopulmonary and in some anterior bronchopulmonary lymph nodes in front of the right main bronchus. Similar, though in general smaller, chalky tubercles were found in the upper part of the right upper lobe, in the subapical area of the left upper, and in the middle and lower lateral areas of both left upper and left lower lobe. There were no chalky or calcified lesions in the lymph nodes draining the left lung. Both lungs were firmly adherent to the parietal pleurae. The pericardial sac was obliterated, and a few chalky tubercles were noticed in the anterior surface of the heart. Gross and X-ray picture suggested primary tuberculosis possibly with several foci of first infection in the right lower lobe and extension of this process to other parts of the right lung and to the left lung. There were no tubercles outside of the lung and the pericardium. The complex was limited to the bronchopulmonary group and the anterior mediastinal lymph nodes on the right side.

Microscopically, these different focal lesions were in considerably advanced state of calcification and hyalinization with very firm encapsulation. All of them showed at least central calcification. In most of them the parallel rings around the central calcified core were very distinct; also the bud-like extensions of larger tubercles within the capsule and a few hyaline satellite tubercles around the capsule. There was no structural difference between the foci in the right and the left lung. Those taken from the left lung showed rather large, hyalinized and calcified conglomerate tubercles attached to the capsule of the larger foci, again in satellite fashion. Only their size was somewhat smaller than that of the three largest foci in the right lower lobe. The lymph nodes draining this lobe showed the same firm, chalky, hyalinized and in part calcified changes that were found in the different pulmonary foci.

The calcification in the pericardium was rather marked. A firm stone had formed near the pericardial surface with early formation of bone along its border. Although these lesions were in a completely obsolete, hyalinized state, there seems to be no doubt that they present a practically healed tuberculous pericarditis in connection with adhesive pleuritis around both lungs.

This case, then, seems to represent the incidental finding of a healing state of focal extensions, apparently caused by intrabronchial spread. Plate 3 shows the roentgen photograph of the lungs and the heart. Note several calcified and chalky tubercles in both lungs, minimal chalky changes in the right bronchopulmonary lymph nodes and several calcified flecks in the right part of the heart. The microphotographs represent two large foci in the right lower and right upper lobe and one smaller focus in the left lower lobe.

In all 5 cases discussed above, the postprimary focal lesions were found in different parts of the lungs with the exception of the apices of both upper lobes; in case 3 in particular, in proximity to the primary focus. In case 1, the huge single additional focus was probably the result of focal hematogenous extension, while for cases 3, 4 and 5 the direct bronchial route was considered the pathway for this focal extension. In case 2, the anatomical findings pointed to different sources for focal extension, through bronchi as well as to clearly established hematogenous seeding to different organs from the primary complex.

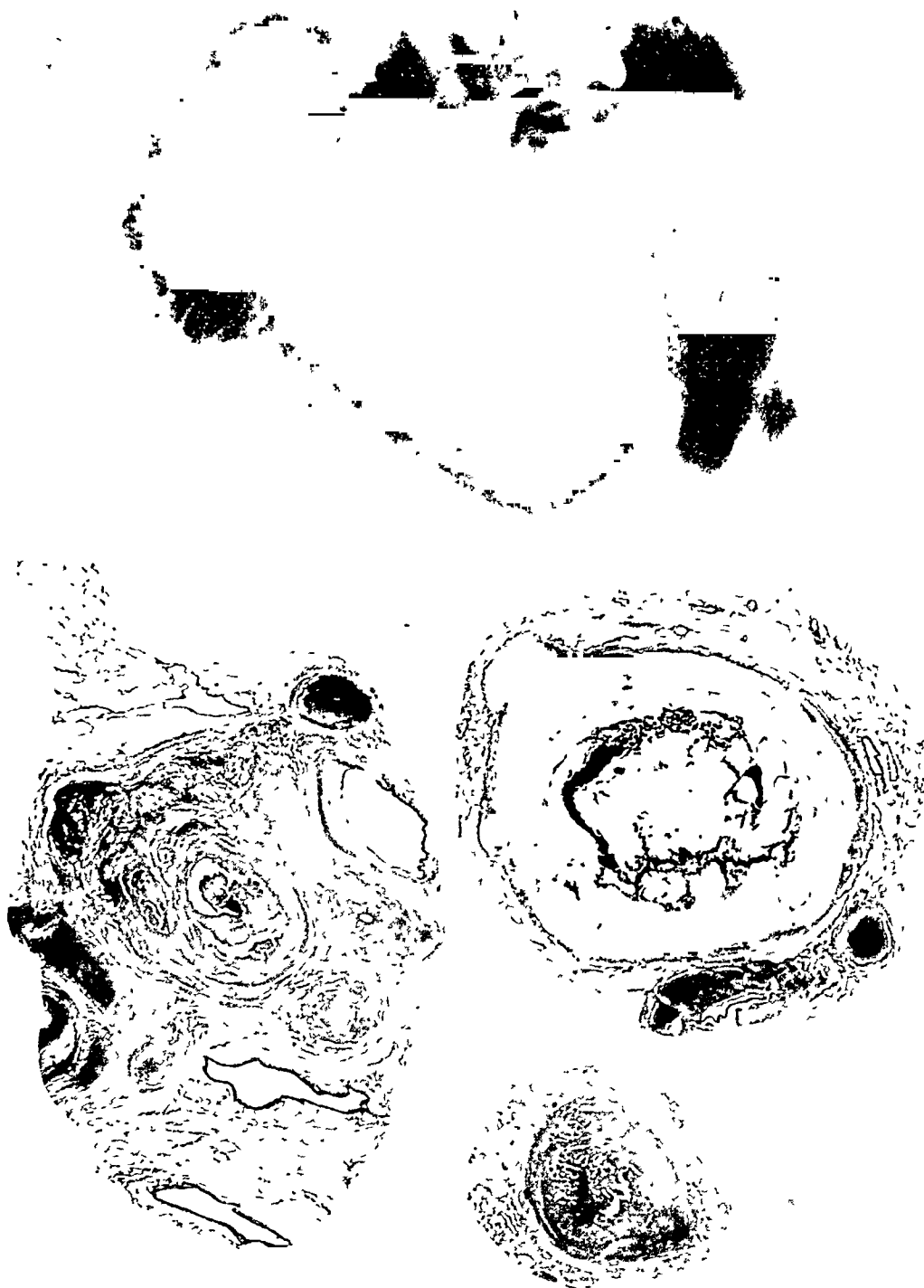


PLATE 3

That any stress on a single pathway leading to these additional focal tubercles would appear arbitrary, is seen from the following incidental postmortem findings in an eight and a half year old white girl (B.G.H. 3268), who died of chronic hydrocephalus of non-tuberculous origin. There was a typical primary complex with a pinhead-sized chalky-calcified focus near the base of the right lower lobe. From the markedly enlarged regional interlobar bronchopulmonary lymph node which was diffusely caseated, the localized progression of tuberculosis through the bulging lymph node capsule into the closely attached lung tissue was clearly visible at gross dissection. In an area of 2 cm. circumference and 0.5 cm. depth, several fibrocaseous tubercles in typical acinous arrangement were seen. The histological study confirmed our impression of the contiguous spread of the lymph node tuberculosis into the lung tissue with closely arranged peribronchial tubercles of pinhead- to small lentil-size. There was distinct disintegration of the caseated centre in the larger tubercles. A small number (about twenty altogether) of fibrocaseous tubercles were found in the lower and upper lobes of both lungs. Their histological structure was similar to that seen in the acinous tubercles surrounding the large caseated right interlobar lymph node. Although the gross picture already seemed to point to scattered aspiration via bronchi from the perihilar acinous tubercles, the presence of a rare fibrocaseous conglomerate tubercle in the spleen did not permit decision entirely against the hematogenous nature of the scattered recent pulmonary tubercles. Several of these were equal in size to the chalky primary focus and were diffusely caseated. It is easy to conceive that later regressive changes within these large postprimary foci might gradually obscure their postprimary character until they are structurally indistinguishable from the true primary focus.

We now shall list the findings in a few cases of the adult group, starting with those in which the primary complex as well as the additional focus or foci in areas outside of the complex were not as yet calcified, but still in a caseated or cheesy-chalky state.

*Case 1:* (B.G.H. 3730) Thirty-nine year old white female. Cause of death: malignant nephrosclerosis. (Plate 4)

*Macroscopic report:* A large pea-sized, well encapsulated, cheesy-chalky tuberculous focus is present in the medium third of the left lower lobe. There are extensive, firm adhesions fixing this lobe to the parietal pleura. There is complete caseation with cavity formation in the left lower tracheobronchial lymph nodes. A few cheesy-chalky nodules are found in the bronchopulmonary lymph nodes at the hilum of the left lower lobe, and a few more recent tubercles in the medial portion of the right lower tracheobronchial lymph nodes in close connection with those below the left major bronchus. Three cheesy-fibrous, round foci are in an area of about 1.5 cm. in diameter in the left subapical field, 1 cm. below the apex. The bronchopulmonary lymph nodes surrounding the hilum of the left upper lobe and the upper tracheobronchial lymph nodes are entirely negative. The histological structure of the primary focus and of the three foci in the subapical area is the same in all of them. They all are surrounded by a fairly thick fibrous capsule and show extensive caseation with chalky changes in their centres. The lymph nodes draining the left lower lobe show extensive caseation with chalky deposits in the centres of the huge conglomerate tubercles.

The photographs of the histological sections (plate 4) show size and structural changes of the foci in question. The capsule surrounding the primary focus is somewhat thicker than in the three foci in the left subapical field and shows also an irregular nodular pro-

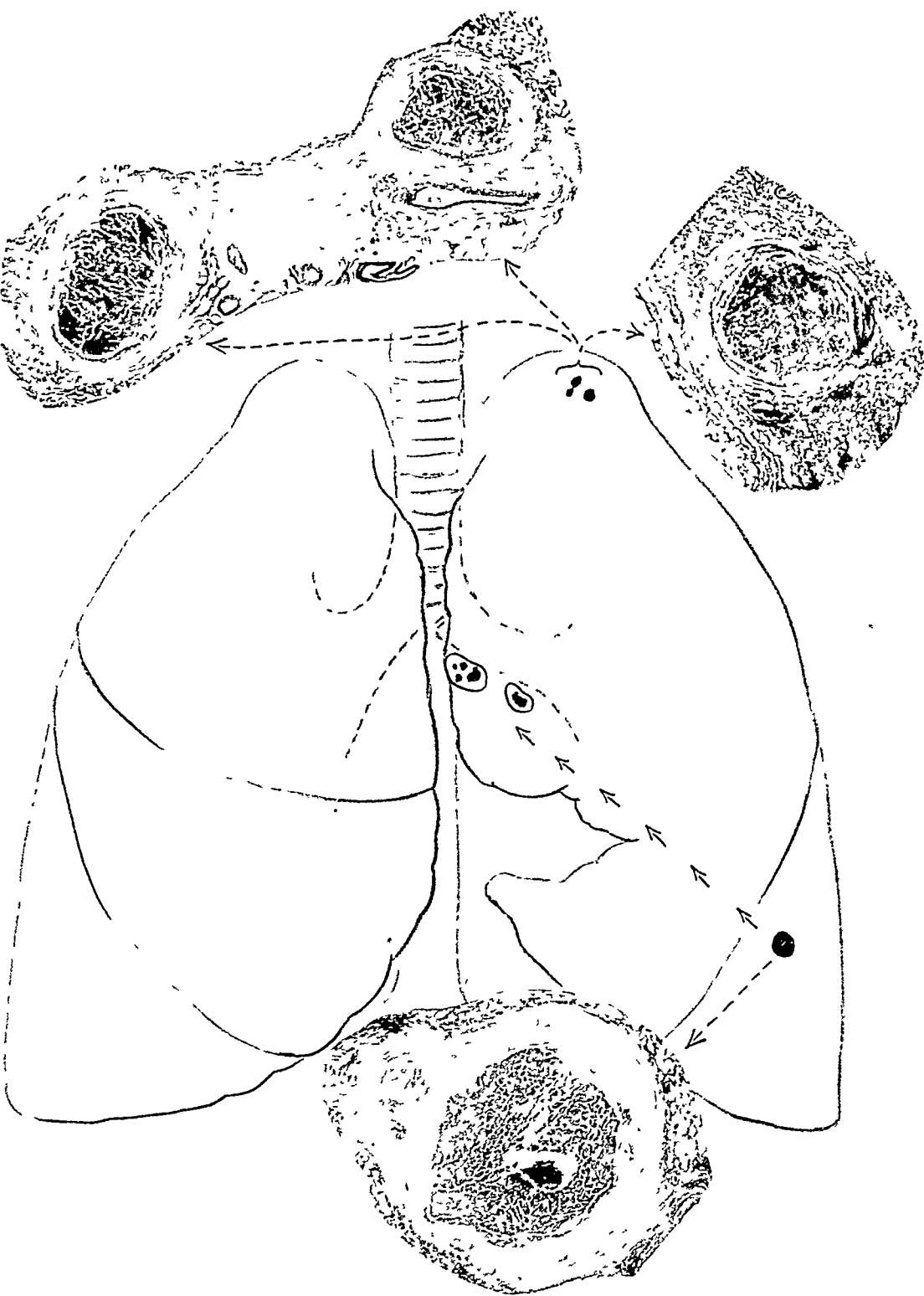


PLATE 4



trusion from a slightly hyalinized tubercle within the capsule. In all four lesions the caseated pneumonic pattern is very distinct. In all of them, in addition, a few cholesterol crystals can be seen in the centre of the firm, chalky-caseated area (not visible in the photographs). The area surrounding the three foci in the upper lobe shows localized atelectasis, as so frequently seen around apical lesions. All lymph nodes draining this area are completely free of tuberculous changes. There are no other tuberculous lesions, neither in the left lung nor in the entire right lung; nor is there any evidence of hematogenous tuberculosis in any organ.

Consistency and histological structure of all four lesions point to a relatively late but typical primary infection of the left lower lobe. All tuberculous lesions, though firmly encapsulated by a hyaline wall, are not as yet calcified; there is some chalky detritus in their centres only. At dissection they all appear soft, not necessitating any decalcifying procedure. Whether the apical lesions were brought about by focal (intra-*bronchial*) extension from the primary focus in its active state preceding encapsulation, or by superinfection after a relatively short interval following the establishment of the primary complex, can hardly be decided. The hematogenous route appears more unlikely in the pathogenetic consideration of the apical lesions in this case.

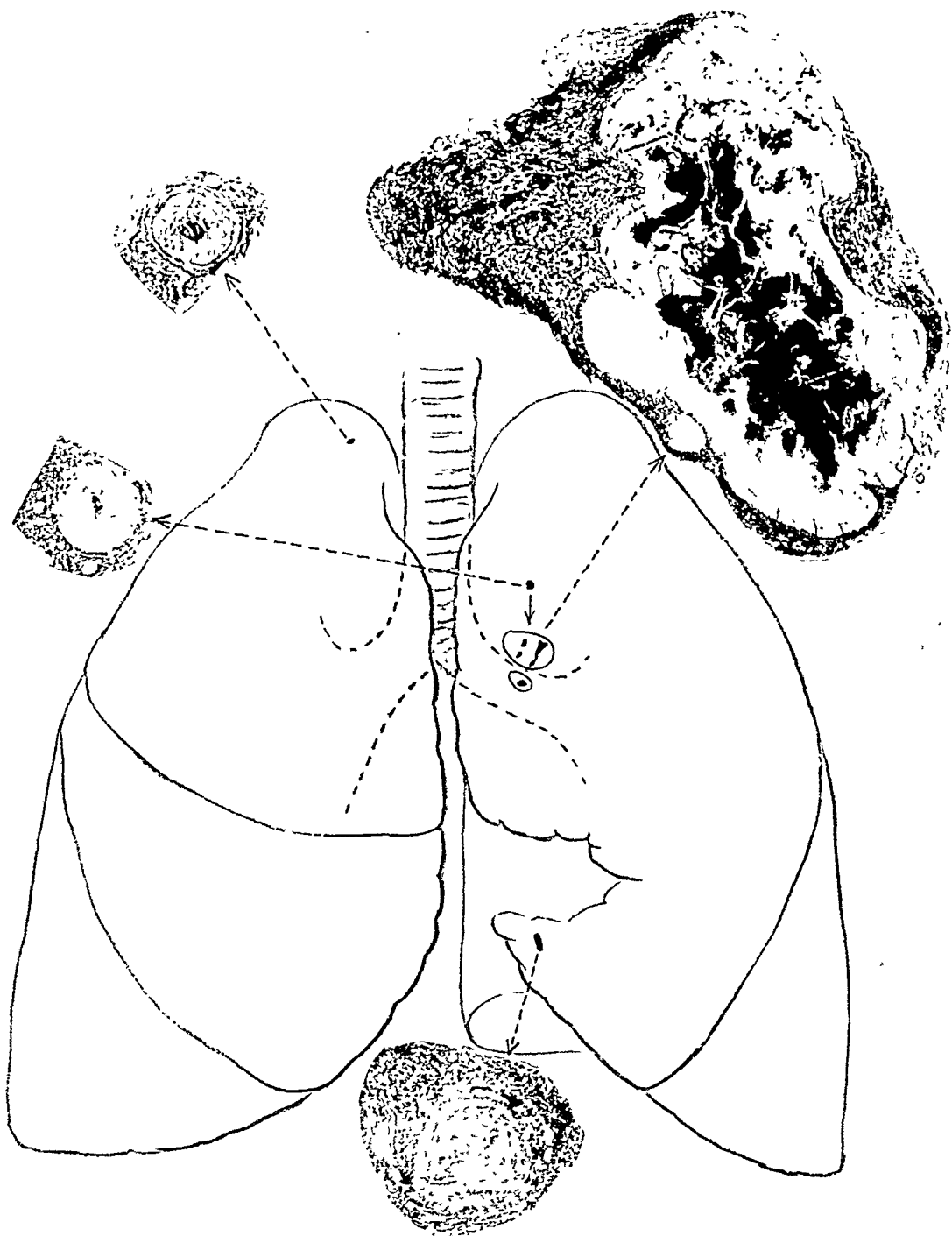
*Case 2:* (B.G.H. 2344) Twenty-eight year old white male. Cause of death: acute perforation of peptic ulcer. (Plate 5)

There are two firm, caseated and well encapsulated foci about 2 mm. in diameter with chalky centres, one in the lingula of the left upper, the other in its upper third near the anterior surface. The anterior bronchopulmonary and mediastinal lymph nodes in front of the major bronchus on the left side contain chalky-fibrous conglomerate tubercles. An additional nodule, only slightly smaller than one of the primary foci in the left lung, likewise with a distinct chalky centre, is found 1 cm. below the summit of the right apex. The histological structure of all three foci shows a firm, caseated pneumonic alveolar pattern with central chalky changes and distinct encapsulation by a moderately hyalinized capsule which is slightly infiltrated by lymphocytes. The bronchomediastinal lymph nodes in front of and above the left major bronchus contain large, caseated conglomerate tubercles with considerable chalky changes and with distinct hyaline, fibrous encapsulation, interrupted by smaller, nodular, hyalinized conglomerate tubercles. There is no stone formation, in fact, the relatively soft chalky material had fallen out at the time of dissection of these lymph nodes. There is no histological evidence of further lymphogenous progression. Most of the smaller tubercles are hyalinized, the larger still in a firm caseated state. The bronchopulmonary lymph nodes draining the right upper lobe are grossly and histologically negative. There is no further finding of tuberculosis in the lungs, nor are there any hematogenous tubercles in other organs.

In this case the structural similarity of all three lesions is even more impressive than in the first one. It is possible that both foci, found in the left upper lobe, in the lingula as well as in the upper third, are primary foci in the real sense. The lymph nodes draining this area, especially the anterior bronchopulmonary group, are tributary to both parts of the upper lobe in which these foci were found. The focus near the apex of the opposite lung is certainly of postprimary nature.

*Case 3:* (B.G.H. 5125) Eighteen year old white male. Cause of death: Addison's disease from progressive cytotoxic atrophy of the adrenal cortex. (Plate 6)

In this case we are dealing with a typical closed, caseated, chalky complex. It consists of a small pea-sized primary focus with a firmly caseated and slightly calcified centre



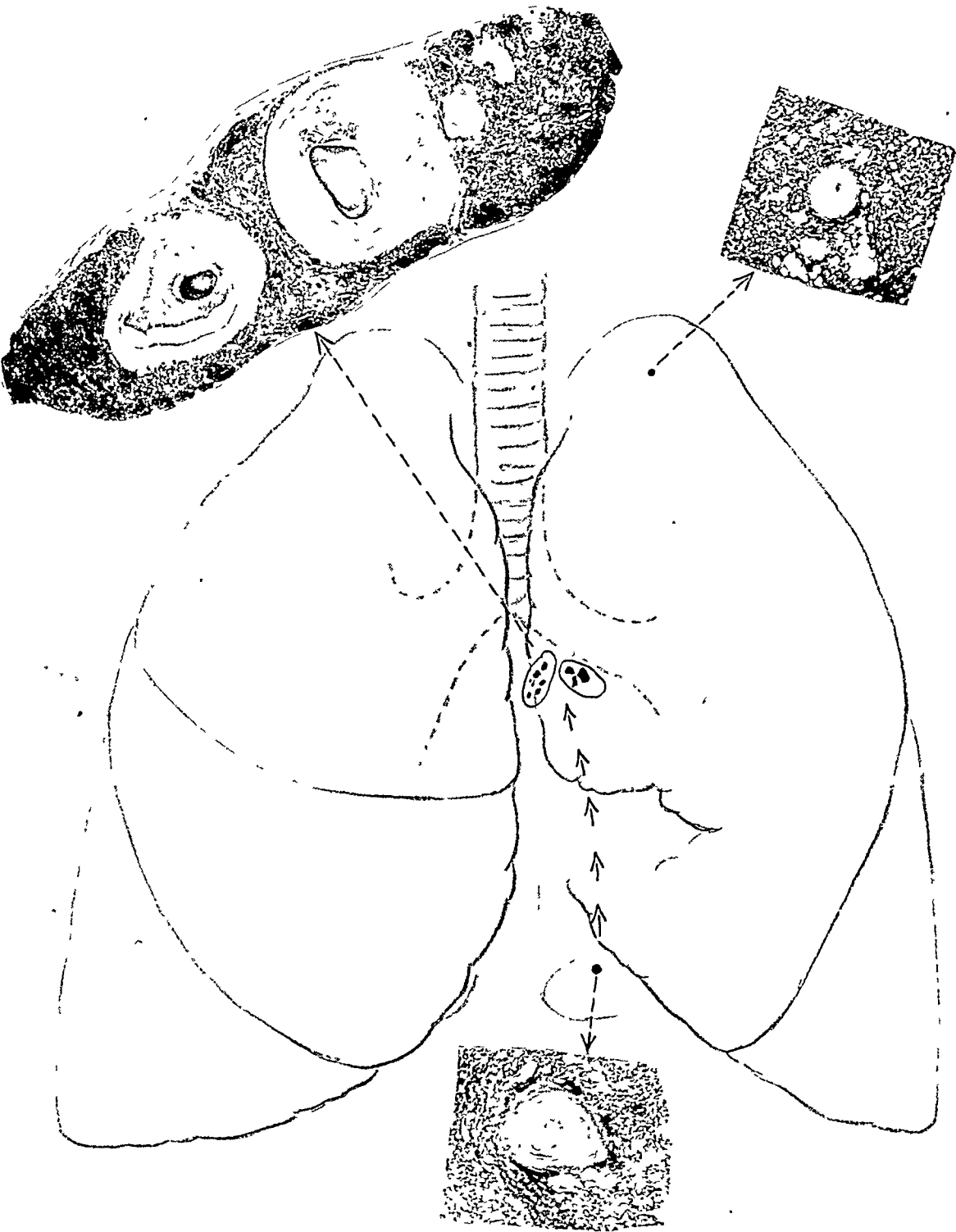


PLATE 6

surrounded by a thick hyaline capsule with a few cholesterol crystals in the periphery of the caseated, chalky core. This focus is found in the base of the left lower lobe near the mediastinal surface, and there are firm, caseated and chalky conglomerate tubercles in the lower tracheobronchial lymph nodes extending slightly to the right side.

The additional focal lesion is presented by a distinctly smaller chalky and slightly calcified nodule in subpleural position at the anterior aspect in the upper third of the left upper lobe. There are no tuberculous changes in the bronchopulmonary and upper tracheobronchial lymph nodes draining the area of the left upper lobe in which this additional focus was found. The nodule in the left upper lobe, though smaller, shows the same structure as that found in the primary focus. There is no stone formation in either. There are no hematogenous tubercles. (Plate 6 shows the entire complex and the additional focus in the upper part of the left upper lobe.)

In the next 2 cases the primary focus and additional foci were already in an obsolete calcified-ossified state.

*Case 4:* (B.G.H. 3826) Forty-two year old white female. Cause of death: primary emphysema. (Plate 7)

A primary focus of small pea-size in firmly calcified state is present in the upper third of the left lower lobe with extensive calcification of two regional interlobar bronchopulmonary lymph nodes. One second, completely calcified focus of exactly the same size is found in the lateral subapical area of the right upper lobe. There are no lymph node changes on the right side. The primary focus and the additional focus of the right upper lobe are, in every respect, of identical histological structure, showing a firm, calcified centre surrounded by a very thin bony shell. The surrounding lung tissue shows irregular localized scarring only at one pole of the additional focus. The two lymph nodes draining the primary focus show likewise considerable ossification, even more marked than in either focus. It is of special interest that in this case with two completely obsolete foci, only one of which is the real primary focus, a second true reinfection occurred. Incidentally, in the subapical portion of the left upper lobe, a firmly caseated focus was found, with little chalky changes, surrounded by a fibrous capsule. This focus of true reinfection did not show any noticeable whitish shadow on the X-ray photograph that might have suggested the little chalky matter which it contained. There were no recent or older changes in any lymph node regional to the subapical area of the left upper lobe.

*Case 5:* (B.G.H. 5079) Thirty-one year old white male. Cause of death: traumatic fracture of the skull. (Plate 8)

In this case there were five structurally identical, firm, calcified foci in the right lung, three in different parts of the subapical area of the right upper lobe, one in the right middle and one in the basal part of the right lower lobe. Only in the bronchopulmonary lymph nodes at the hilum of the right lung, just anterior to the angle between the bronchi to upper, middle and lower lobes, there was compact calcification; a minute calcified nodule in one right lower tracheobronchial node was also seen. All five foci were of the same size, varying in diameter from 1 to 1.5 mm. Histologically they were typical stony foci with a thin bony shell, well encapsulated. In one of the bronchopulmonary lymph nodes there was likewise some bone attached to the stony matter. There were no tuberculous lesions in the left lung and no fibrous or calcified tubercles in other organs.

It cannot be decided whether all of these five foci are primary in the strict sense. The massive calcification of the bronchopulmonary lymph nodes at the hilum of the right lung

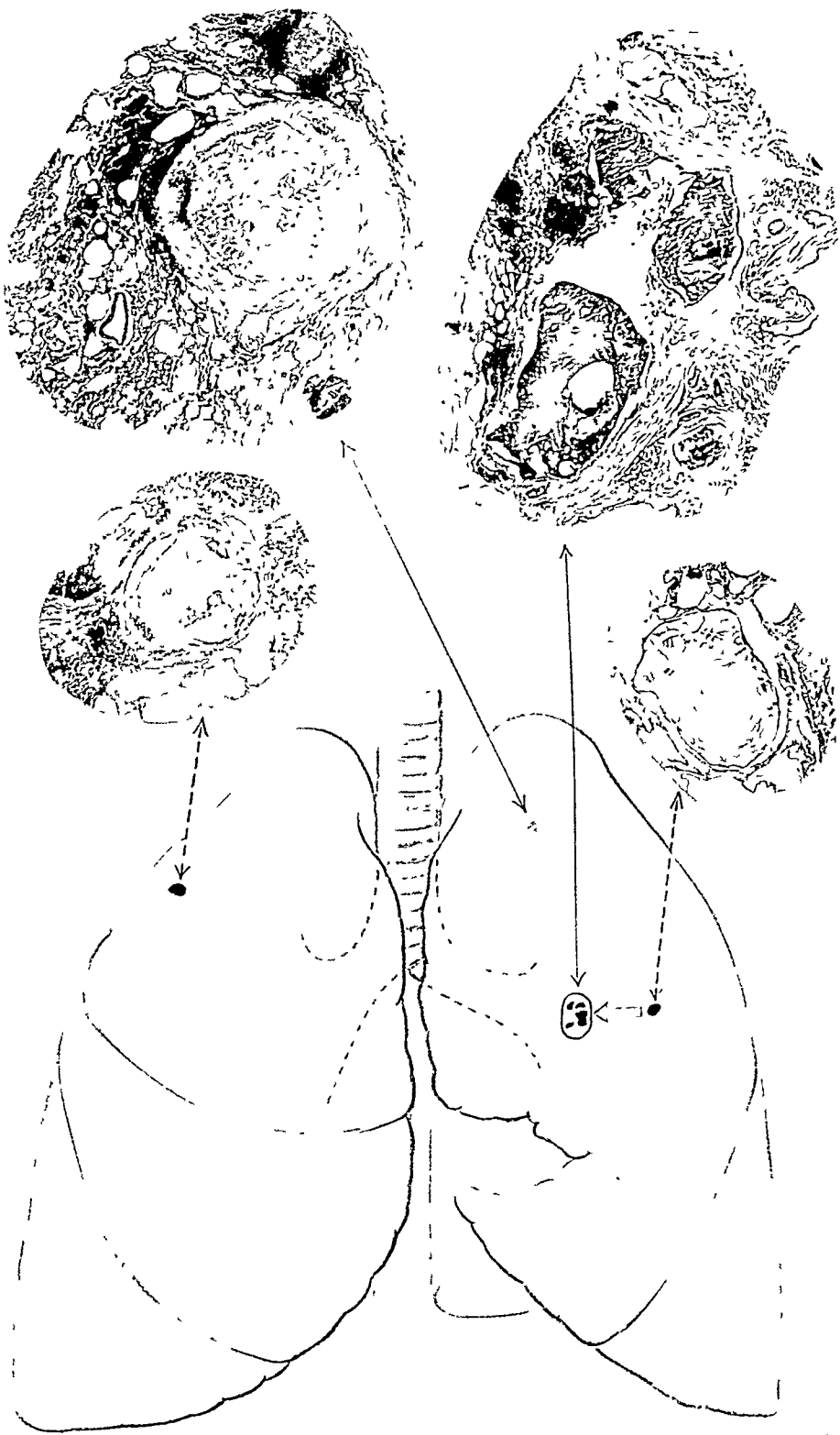


PLATE 7

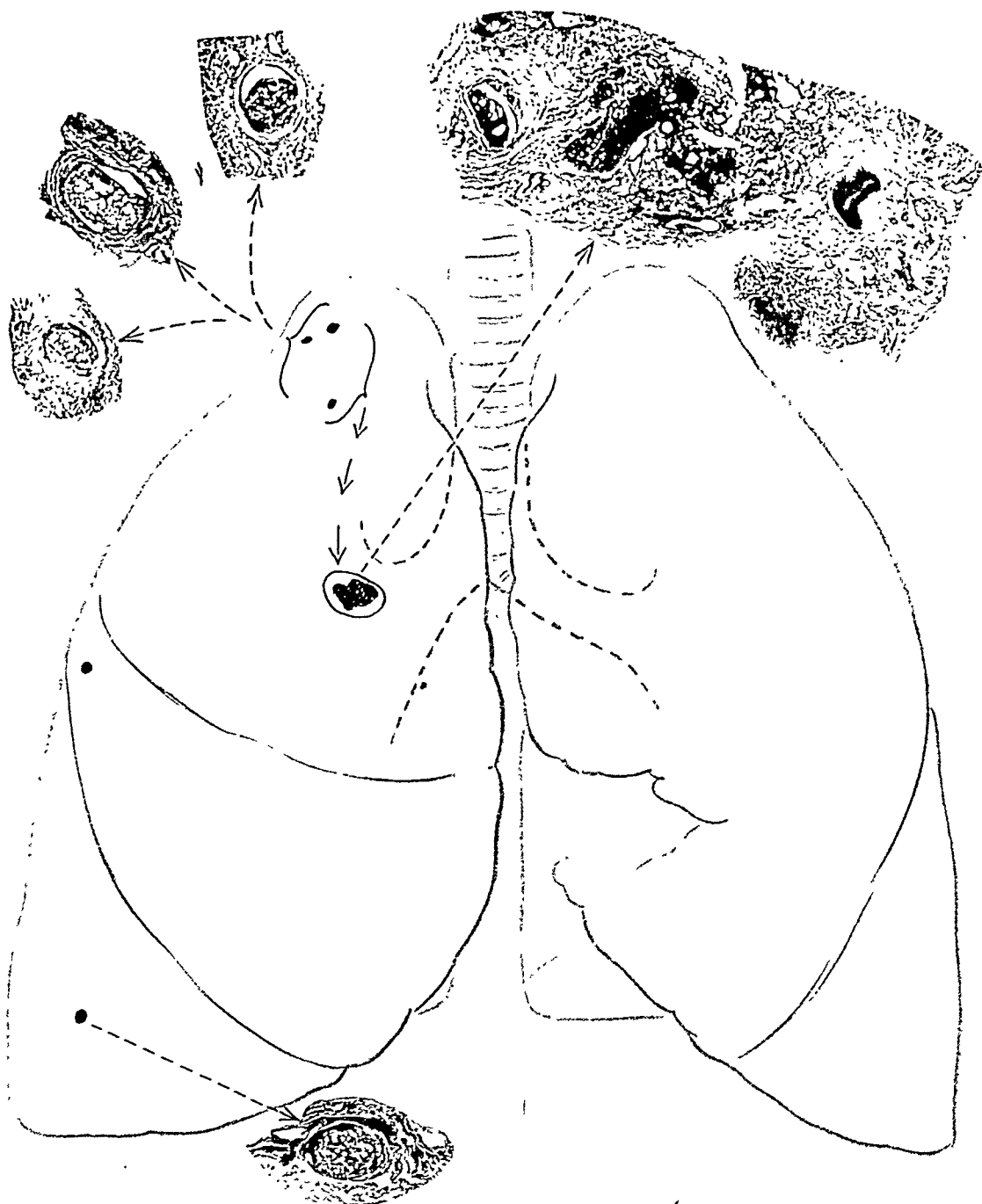


PLATE 8

could be tributary to all fields in which these five lesions were found, although—according to our past experience—they seem to drain primarily the upper field.

The next case, presenting a relatively late primary infection, seems of special interest, inasmuch as in addition to one large pea-sized focus in the left lung of the same histological structure as that found in three large primary foci in the right lung, with a fairly massive complex, there were scattered, small cheesy-chalky tubercles in different parts of the lung and a few tubercles in the liver, proving hematogenous seeding of apparently quite restricted type.

*Case 6:* (B.G.H. 5004) Thirty-eight year old white male. Cause of death: pneumococcic meningitis. (Plate 9)

There are three hazelnut-sized, firm, cheesy-chalky, well encapsulated foci in the basal portion of the right lower lobe with very numerous fibrous subpleural tubercles of average hemp-seed size in the area of the three foci. The lymph nodes at the hilum of the right lower lobe show extensive chalky-caseated changes with soft caseation and cavity formation in one right lower tracheobronchial node. These complex changes do not extend beyond the lower tracheobronchial group. In the left lower lobe there are two additional cheesy-chalky foci one of them 3 to 4 mm. in diameter and exactly of the same anatomical structure as the foci in the right lung. The other focus, about 2 mm. in diameter, appears less firm than the former. Both, however, contain a considerable amount of chalky material. These two foci are likewise surrounded by a few subpleural tubercles, just like the foci in the right lower lobe. There are a few small subpleural tubercles of pin-head-size also in the right upper lobe. The upper tracheobronchial lymph nodes on both sides and the paratracheal group are grossly normal. Except for the marked chalky-caseated changes in the lymph nodes, surrounding the bronchus of the right lower lobe, there is no grossly noticeable tuberculosis in any lymph node group and especially not in the lymph nodes draining the left lung. There is distinct evidence of hematogenous tuberculosis in the liver, with a few fibrous subcapsular tubercles about 1 mm. in diameter.

In this case, again, it cannot be decided whether the three foci in the right lower lobe are primary in the strict sense or whether one of them is the oldest focus while the other two within a radius of 2 to 3 cm. developed in connection with this first lesion. There is, however, no question that the two foci in the left lower lobe are not part of the primary complex, and, as in the previous cases, there is no further spread to lymph nodes draining the left lower lobe. Especially the larger one shows exactly the same structure as the three primary foci, namely a well encapsulated, fair sized, chalky, calcified centre surrounded by a broad collagenous band. Even in this chalky-calcified state it is evident that the largest of the three foci in the right lower lobe shows finger-like protrusions from its capsule into the surrounding tissue. These, too, are in a state of firm chalky-fibrous regression. The scattered small subpleural tubercles, which are not calcified and found on gross dissections, are hematogenous metastases, as are similar tubercles found in the liver. The source for this hematogenous seeding seemed to be present in the cavitation of the right lower tracheobronchial lymph nodes. Here, then, there is a combination of this peculiar focal extension to the opposite lower lobe with restricted hematogenous spread forming scattered miliary tubercles in the lung as well as in the liver. There are no apical lesions whatsoever. This case also represents a state in which the tuberculous process is apparently still active in the lymph nodes of the complex, while it has obviously healed in the three large primary foci tributary to the lymph node changes.

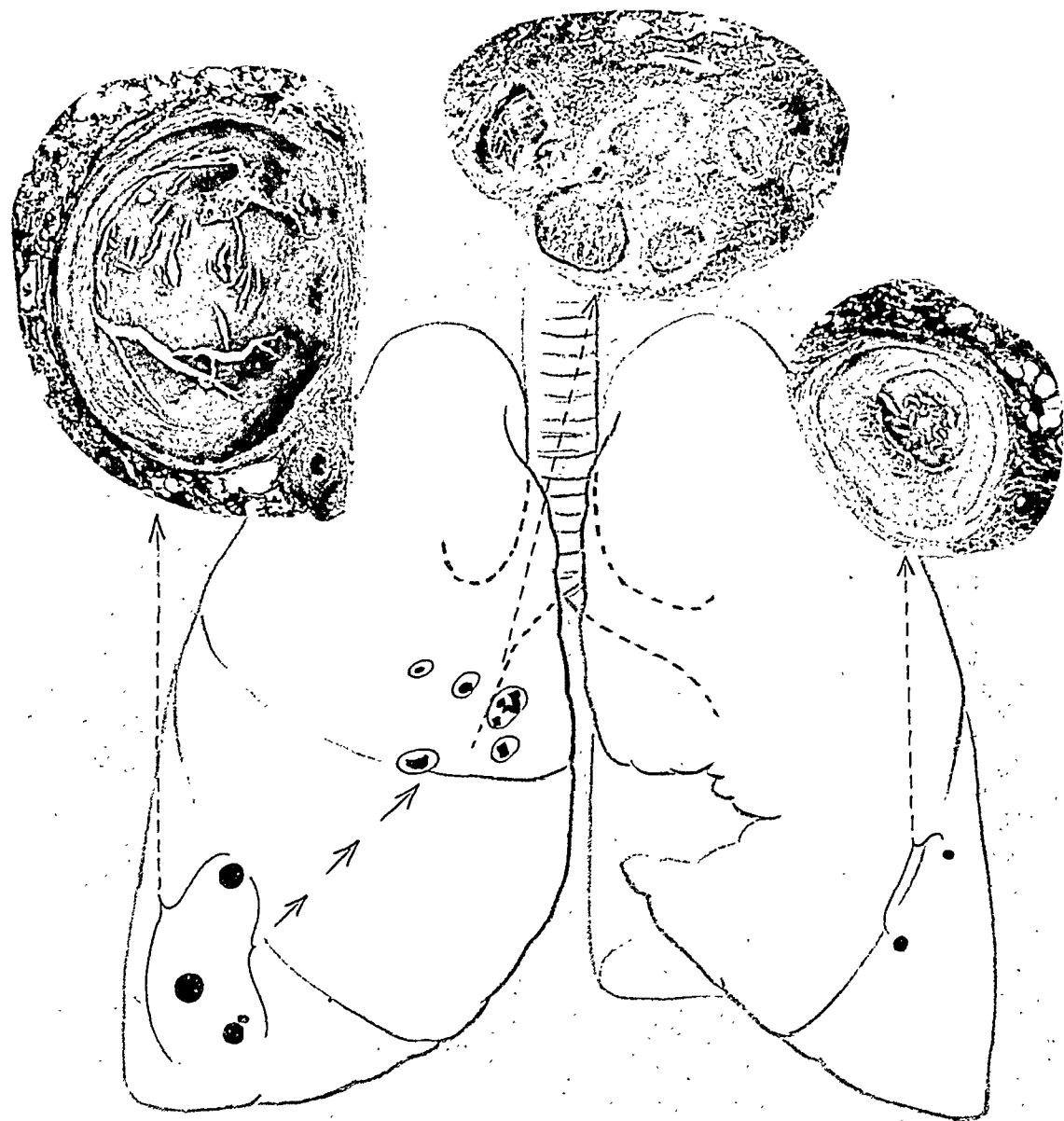


PLATE 9



In one other case, *no. 7* (B.G.H. 2360), five calcified-ossified foci were found in an area of about 2 cm. radius in the right lower lobe with old stony tuberculosis of the regional lymph nodes, and three entirely identical foci—in structure and size—in the lower and upper lobe of the left lung below the hilar level. Here, the distribution of all these foci seems to point to perifocal spread and focal extension by intrabronchial spread rather than to superinfection.

A similar interpretation might be given in the following case, *no. 8* (B.G.H. 4180), a forty-five year old white male who died from a chordoblastoma encroaching upon the pons. (Plates 10a and 10b)

This case presents the anatomical findings of an apparently late primary tuberculous infection with about ten cheesy-chalky foci in different parts of the right middle, right lower and in the lower part of the right upper lobe, and with two additional foci of similar size and character in the middle third of the left upper and the base of the left lower lobe. Their sizes vary from 4 mm. in the smaller to 6 to 7 mm. in the larger lesions. Several lymph nodes within the right bronchopulmonary and lower and upper tracheobronchial groups containing conglomerate cheesy-fibrous tubercles complete the primary complex. Whether or not there was one or more real primary foci somewhere in the right lung could not be decided, neither by gross nor by histological analysis. In addition, a few isolated, miliary fibrous tubercles were found in the spleen. All lymph nodes regional to the left lung were normal. Outside of the large foci there were no tubercles present in the lungs. The histological structure of all these foci was uniformly the same: a typical picture of caseated pneumonia in beginning fibrous organization with a typical elastic tissue pattern and but slight chalky changes in the centre.

It is of special interest to note that the focus in the base of the left lower lobe is of considerable size (between 6 and 7 mm.), which is equalled by only one of the "primary" foci in the right lung. The close proximity of several tuberculous lesions in the right middle and in the base of the right lower lobe, and the fact that most of the other single foci are near the hilar level in the right upper lobe suggest that some of these might have resulted from focal intrabronchial extension. This, we feel, is also responsible for the two large single foci in the left lung, in spite of the fact that a few miliary tubercles in the spleen prove that hematogenous seeding of tubercle bacilli was present in this case. There were no tubercles, small or large, in the apical or subapical field of either lung.

The anatomical findings are somewhat similar in *case 9* (B.G.H. 2108), a forty-six year old white male. Cause of death: Grave's disease.

In this case we are dealing with two primary complexes, one in each lung. There are six large pea-sized, calcified, chalky tuberculous foci in subpleural position in different parts of left upper and lower lobes, two in the upper third, one in the centre, one between middle and lower third of upper and two in the lower lobe, about 5 cm. above the base in subpleural position. Only the anterior bronchopulmonary lymph nodes in front of the left major bronchus show chalky and slightly calcified changes, surrounded by some firm, caseated-fibrous tubercles. The left upper tracheobronchial nodes show extensive cheesy changes with slight cavity formation and more isolated, caseous fibrous conglomerate tubercles. The interlobar lymph nodes between left upper and lower lobes show also older, caseous-chalky changes with central disintegration.

Size and location of the focal lesions in the right lung are as follows: a small bean-sized focus with a central cavity containing caseous-chalky detritus in the upper third of right upper; a large pea-sized focus in anterolateral part of right middle; two small pea-sized,

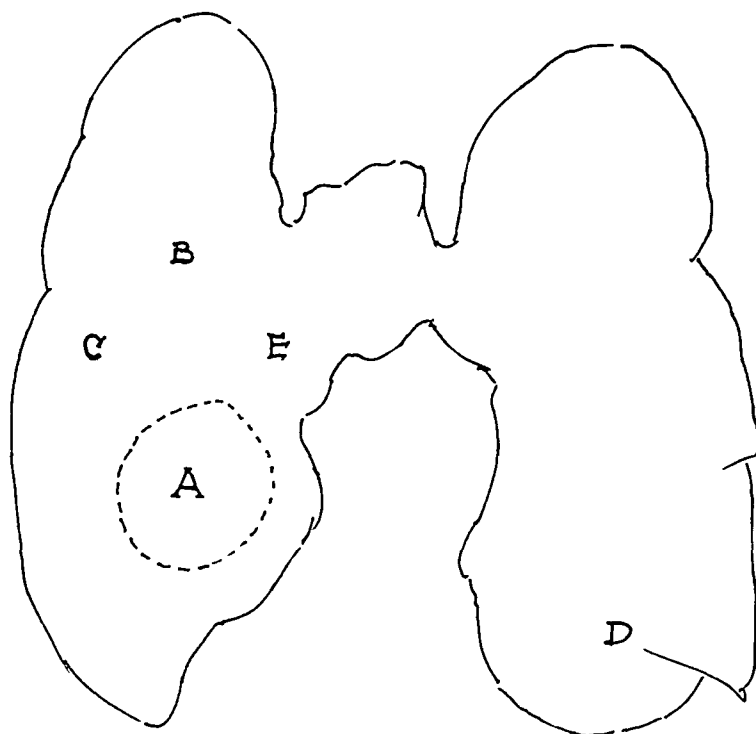


PLATE 10a



PLATE 10b

encapsulated, chalky foci in the upper third of the right lower lobe near the hilum; and a somewhat smaller lesion in the base of this lobe near the anterior mediastinal margin. There are slight chalky changes and a few grayish tubercles in the interlobar lymph nodes between right upper and lower lobes.

The histological examination of all focal lesions in both lungs shows a uniform histological structure with a caseous chalky centre within a distinct fibrous capsule. The corresponding cheesy-chalky lymph node changes were typical, with active tuberculous granulation tissue near the large caseated areas. These active changes were more marked in the pretracheal and paratracheal lymph nodes. It was noticed already at gross inspection that one of the foci in the right upper lobe showed a short, pipe-like appearance with a central cavity, apparently replacing a smaller bronchus. In all, there were nine typical, firmly caseated, chalky and slightly calcified foci, six in the left and three in the right lung. All of these had the same structure and there was but little difference in their size. The larger ones showed distinct central cavitation. There were no tuberculous changes in the bronchopulmonary lymph nodes at the hilum of each lower lobe and in the lower tracheobronchial groups on both sides. How many of the foci in the areas drained by the two lymph node groups showing caseous, chalky changes are primary in the true sense we naturally could not determine. The foci, however, in the lower lobes, especially in those areas which normally are drained by the bronchopulmonary groups at the hilum of these lobes and by the lower tracheobronchial group, are not primary foci in the strict sense, but are obviously postprimary lesions in spite of their similarity in structure and size with the foci in the upper lobes, especially with those forming the complex in the left lung. The fact that in the two largest foci detritus-like remnants of a cavity were found, surrounded by a distinct cheesy pneumonic structure, could point to an early intrabronchial spread by which tubercle bacilli were aspirated into other parts of the lung, forming the lesions in the lower lobes. These two large foci appeared, in addition, in very close topographic relation to the chalky bronchopulmonary lymph nodes in front of the left major bronchus and to one interlobar lymph node regional to the right upper lobe. In the latter the tuberculous process was much less marked. There were no focal lesions, large or small, in the apices and in the subapical areas. The uppermost lesions in both upper lobes were about 5.5 cm. below the apex. There were no hematogenous tubercles noticed in any organ. (One single phlebolith, however, is mentioned in the macroscopic description of the spleen. As a histological control of this lesion was unfortunately omitted, it is possible that this "phlebolith" might have been a single hematogenous tubercle.)

Our series includes 2 cases with the typical picture of healed tuberculosis of the mesenteric lymph nodes. In each of these a few isolated, minute, firmly calcified tubercles were found in different parts of both lungs—six in one, and four in the other case. They are obviously healed metastases. There was no lymphogenous spread from these metastatic foci. In both cases these isolated hematogenous tubercles were very small; in one case hardly visible on the X-ray film, in the other about 1 mm. in diameter, or less. The histological picture corresponded, in all of these minute lesions, to the obsolete, calcified-ossified state of a typical primary focus, showing the alveolar pattern, a complete bony ring, here and there with some marrow.

The entire anatomical material presenting isolated additional postprimary foci in the presence of a typical complex change is arranged in the accompanying tables 1 and 2. Table 1 shows, in comprehensive fashion, the distribution of these few focal lesions in the presence of a typical primary complex.

TABLE 1  
*Focal extension*

TO APICAL OR SUBAPICAL AREAS	TO DIFFERENT PARTS OF LUNGS	TO AREA AROUND PRIMARY FOCUS (PERIFOVAL)	CLEARLY HEMATOGENOUS METASTASES
5125—same apex	5079—same side	3331	4180—few tubercles in spleen, apices negative
3730—same apex	5004—combined with recent hematogenous spread	5224—also to one apex 2274	4920—6 small foci in lungs from primary intestinal
2260—same subapical area	2930	3239—multiple, partly in bronchi	2343—4 small foci in lungs from primary intestinal
3762—same subapical area (several foci)	2196		2108—phlebolith (?) in spleen, apices negative
2228—each apex			
5286—each apex			
2661—each subapical area			
2344—opposite apex			
3826—opposite apex	2108—possible hematogenous		
3353—opposite apex			
2141—opposite subapical areas	4766—also perifocal	4766	
2074—opposite subapical areas	2360—also perifocal	2360	
2113—opposite subapical areas	4978		
2745—opposite subapical areas	2759		
2232—opposite subapical areas	4640		
	2353		
	2224		
	2157		
	2292		
	4856		
	5386		
	3776—single opposite lower		3776—a few tubercles in spleen
	2309		

TABLE 2  
*Focal extension in cases with reinfection complexes*

TO APEX OR SUBAPICAL AREA	TO DIFFERENT PARTS IN LUNGS	TO AREA AROUND PRIMARY OR REINFECTION FOCUS (PERIFOVAL)	HEMATOGENOUS
5256—same apex (from old focus)	5301—from reinfection focus	4932—around reinfection focus	
5123—opposite subapical area (from old focus)			
4757—opposite subapical area (from old focus)			
5131—same subapical area (from reinfection focus)			
4621—same subapical area (from reinfection focus) also old foci in both upper lobes			4621—recent tubercles in spleen and liver
4776—opposite subapical area (from reinfection focus)			

Special Active Case

5407—both subapical areas, especially left	5407—overwhelming military to all lobes	5407—distinct perifocal extension	5407—overwhelming military to lungs, spleen, liver, peritoneum, brain and leptomeninges
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Of 41 cases, in 15 the focal lesions, only few in number, were near the apical area or in the subapical field, four times on the same side as the focus, four times in both apical or subapical areas, and seven times in the apex or subapical

field of the opposite lung. In 16 cases a few of these focal lesions were found in different parts of both lungs. In 6 additional cases there was a very distinct perifocal spread around the primary focus, forming several lesions of the same size as the primary focus. In one of these, some of the additional foci were found in the lumen of smaller bronchi. Only in 4 out of the entire series there seemed to be clear evidence of scattered hematogenous seeding with formation of a few small miliary tubercles.

One case in table 1 deserves special citation (B. G. H. 2113). In this case the primary focus, as well as the additional single focus which was of the same size and was found in the opposite lung, had reached the same unusual state of final replacement of the original caseated lesion by a fibromatous scar. Calcification was present only in the two lymph nodes forming the primary complex.

In all the cases so far discussed, we were dealing with a typical primary complex. In our observations on reinfection complexes we could demonstrate similar findings of this focal extension, either in connection with the focus of reinfection or from the old focus of the first infection. These findings are tabulated in table 2. In 5 of these cases there were recent lesions of the same structure as the reinfection focus. In 3, the additional foci showed the structure of the primary focus. In 6 of these 8 cases, these foci were found in the apical or subapical areas, mostly in only one upper lobe of the same or the opposite lung. In only one case was there secondary extension from the reinfection focus to different parts of both lungs without any evidence of hematogenous spread, and in another case this secondary spread was restricted to the area around the reinfection focus. Hematogenous tubercles in the spleen and liver, of recent nature, were found only in one case which showed a single additional focus in the subapical area of the same structure and on the same side as the reinfection focus.

In the first 3 cases, of the children's group, previously discussed, a combination of acutely progressive hematogenous tuberculosis with these peculiar findings of focal tuberculosis apart from the primary complex was presented. It was also shown (in case 3) that localized intrabronchial spread in more or less direct connection with the primary focus might be responsible for this restricted focal extension or even for localized atelectasis in connection with endobronchial tuberculosis. Most of these anatomical lesions associated with one or more primary complexes, however, are primarily of morphological interest. Being of accidental nature they had not led to disease and death from tuberculosis.

By whatever route these postprimary lesions might have formed, whether by intrabronchial or hematogenous focal extension, or by superinfection, or as scattered miliary hematogenous metastases, their structures, especially as revealed in the later involutionary stages, was uniformly the same. This detailed examination, then, has proved that the structures of these focal tuberculous lesions are of no decisive diagnostic significance relative to their pathogenesis. In the course of these studies it was quite frequently a surprise to find that these lesions, often in no apparent topographic relation to the primary focus, had none-the-less the structure of a primary focus.

TABLE 3  
Forty-nine cases with focal extension

CASE NUMBER	AGE	RACE AND SEX	STATE OF PRIMARY COMPLEX	SITE AND NUMBER OF PRIMARY FOCUS OR FOCI	NUMBER AND LOCATION OF ADDITIONAL FOCI OF PRIMARY FOCUS STRUCTURE	VARIOUS OTHER FINDINGS INCLUDING HEMATOGENOUS METASTASES OR REINFECTION FOCI
5125	18	White M	Caseated-chalky	Single—base left lower	Single—upper third, left upper	None
4856	23	White F	Chalky	2 foci in different parts of left lower		None
2343	23	White F	Primary calcific, mesenteric	None	4 calcified miliary lesions in different parts of both lungs	The miliary tubercles in both lungs are hematogenous metastases
2344	28	White M	Chalky-fibrous	2—lingula and middle third, left upper	1—1 cm. below apex of right upper	None
5079	31	White M	Firmly calcified	3—right upper	2—right middle and right lower	Only lymph nodes above the right major bronchus in the hilar area of the right upper lobe, showing firm calcification
5004	33	White M	Cheesy-chalky, fibrous	3—base right lower	2—midportion of left lower	Few miliary, caseated-fibrous hematogenous tubercles, right upper, left lower, liver and right kidney. Cavitation in one lymph node of primary complex
2930	36	White F	Firmly calcified	2—left lower	2—left upper, right middle	None
2274	38	White M	Stony, ossified (2, complexes)	Upper part left upper; base right lower	3 ossified foci around primary focus left upper	None
3730	39	White F	Caseated-chalky	Single—medium third, left lower	3—1 cm. below apex left upper	Cavity formation in the caseated lymph nodes of complex
4920	40	White F	Calcified	Primary intestinal tuberculosis	6 miliary calcified foci in left upper, right lower and right upper	The miliary calcified tubercles in the lungs are hematogenous metastases
3826	42	White F	Firmly calcified	Single—upper third, left lower	Single—subapical area, right upper	Single caseated, chalky focus of true reinfection, subapical area, left upper
5224	42	White M	Firmly calcified	Several foci base left lower	Several lesions in area of primary focus, also one single additional lesion in right apex	No hematogenous spread
2228	43	White F	Calcified, ossified	Single—middle third, left lower	2—about 1 cm. below apex of each upper	None
3353	43	White F	Firmly calcified	Single—left lower, not found; a minute shadow pointing to calcification on X-ray film	Single—subapical area, 2 cm. below apex, right upper	None
2141	44	White F	Firmly calcified	Single—base right lower	Single—middle third, left upper	None
3331	44	White F	Firmly calcified with bone formation	Several—lingula left upper	Irregular, perifocal spread in area of primary focus	None
2196	45	White F	Firmly calcified	2—lower third left lower	Single—upper third right lower	None
4180	45	White M	Caseated-chalky	Several—right lower, right middle, medium third, right upper	Several—base left lower and upper third left upper	Few small hematogenous tubercles in spleen. No tubercles in apices

TABLE 3—Continued

CASE NUMBER	AGE	RACE AND SEX	STATE OF PRIMARY COMPLEX	SITE AND NUMBER OF PRIMARY FOCUS OR FOCI	NUMBER AND LOCATION OF ADDITIONAL FOCI OF PRIMARY FOCUS STRUCTURE	VARIOUS OTHER FINDINGS INCLUDING HEMATOGENOUS METASTASES OR REINFECTION FOCI
2074	46	White M	Firmly calci-fied	Single—middle third, left upper	3—middle and lower third, right upper	None
2108	46	White M	Caseated-chalky (2 complexes)	Several—left upper, right upper	Several foci in both lower lobes	None
2745	46	White F	Fibrous-chalky	Single—lower third left upper	Single—lower third right upper (fibrous-chalky)	None
3239	46	White F	Firmly calci-fied	Several—left lower	About 12 foci in hilar area and base of left lower, some of them in intrabronchial location	None
2260	49	White M	Calcified, ossified	Single—base right lower	3—right upper above level of bronchus	None
5131	50	White M	Reinfection complex caseated-chalky	Single—middle third, left upper	Single—subapical area left upper	In the presence of one old, stony complex in right lung
4766	53	White F	Firm, stony	Single—right lower	Single—left lower	Also old perifocal spread with several small tubercles
3776	54	White F	Cheesy-chalky	Single—base left lower	Single—upper part of right lower	A few hematogenous tubercles in the spleen
4932	54	White F	Caseated	Single—center left lower	Several huge tubercles around focus in connection with smaller bronchi	Considerable perifocal spread around reinfection focus
2360	55	White F	Firmly calci-fied	5—base right lower in close proximity	3—middle third, left lower, lower third left upper	None
2661	55	White M	Cheesy-chalky	At least one, subapical right upper	Several foci in right subapical area and one in the left subapical field. Lymph nodes on left side negative	None
2232	55	White F	Caseated-chalky, fibrous	Single, lower third, right lower	Single—left subapical area	Old central cavitation in primary focus
4757	55	White F	Stony, ossified	Old focus in right middle	Single focus in left upper	Complexes of different age
3762	56	White F	Chalky-calcified	Single focus right lower	To right subapical area, several chalky-calcified foci	Also primary intestinal complex, calcified
5123	56	White M	Firmly calci-fied	Single—base right lower	Single—left subapical	In the presence of recent reinfection complex in left lower
4978	57	White M	Firmly calci-fied	Single—right middle	Single—base left lower	None
2759	57	White F	Firmly calci-fied	Single—middle third, left upper	Single—middle third left lower	Lymph node change restricted to one bronchopulmonary lymph node above left major bronchus
4640	62	White F	Firmly stony	3—right middle (lower and uppermost portion of this lobe)	Single—base, left lower	None
4776	62	White F	Chalky-caseated	Single—base right lower (from reinfection focus)	Single—left subapical area	Complexes of different age
2309	65	White F	2—stony, calcified	Right lower and left lower	About 3 foci in different parts of right lung and one in left lung	None



TABLE 3—*Continued*

CASE NUM- BER	AGE	RACE AND SEX	STATE OF PRIMARY COMPLEX	SITE AND NUMBER OF PRIMARY FOCUS OR FOCI	NUMBER AND LOCATION OF ADDITIONAL FOCI OF PRIMARY FOCUS STRUCTURE	VARIOUS OTHER FINDINGS INCLUDING HEMATOGENOUS METASTASES OR REINFECTION FOCI
2353	66	White F	Firmly calci- fied	Single—lower third, right up- per	Single—basal portion left lower	None
2113	66	White F	Stony	Single—left upper	Single—middle third right upper	Primary focus and additional focus in opposite lung, pre- sented by hyalinized, fi- brous scar
5256	66	White M	Stony-ossified	Single, left upper	Single—left apex (from first infection focus)	Complexes of different age
5286	69	White F	Stony-ossified	Single—left lower	One to right apex, 2 to left apex	None
2224	70	White F	Firmly stony	2—midportion right lower	Single—base left lower	None
2157	72	White M	Stony-ossified	2—lower part left upper	Single—midportion right lower	Extensive complex formation crossing over to right para- tracheal group
5386	73	White F	Stony-ossified	Single—base right lower	Single—base left lower	None
4621	74	White F	Caseated- chalky (re- infection complex)	2—base left lower	Single—upper third left upper	3 old ossified foci in right up- per and one in left upper. Also recent hematogenous tubercles in spleen and liver
5301	74	White M	Caseated- fibrous	Single—middle third, right upper. A few small caseated-chalky tubercles in lingula of left upper		Old stony complex likewise in the right upper
2292	85	White F	Firmly ossified	Single—left lower	2—right upper and right lower	Complex restricted to pul- monary lymph nodule in left lower and left broncho- pulmonary group
5407	22	White F	Recent casea- tion	Subapical and midportion, left upper, 1-3 pri- mary foci	Two in each subapical field, on the left side close to the primary foci	Dense miliary in both lungs, with recent lymphogenous progression, hemorrhagic pleuritis. Miliary tuber- cles in spleen, peritoneum, liver, white matter of the brain. Tuberculous men- ingitis

Of the 49 cases listed in the tables and the 6 cases of the children's group individually described, complete histological analysis of all focal lesions was carried out without exception. In all of these cases, careful microscopic search for hematogenous tubercles, especially in such organs as the spleen, liver and kidneys, was made; suspicious nodular structures or infiltrates were routinely examined microscopically. As the table shows, there were only a few instances in which hematogenous tubercles were found in the spleen or liver, and 2 other cases with obviously hematogenous tubercles in the lungs secondary to a primary intestinal complex with considerable calcification in the mesenteric lymph nodes. The size of these obsolete hematogenous tubercles as well as of the more recent tubercles of apparently hematogenous nature was, in these cases, of the small miliary type, considerably below the volume of the larger focal lesions. In all of these cases with definitely proved evidence of hematogenous spread, although of a distinctly restricted manner, there was no predilection for the apices. The larger focal lesions found in these cases, with some hematogenous

spread to organs outside of the lung, were also below the level of the apex and the immediate subapical area. That in some of them (especially in cases 2108 and 4180) central cavitation in one of the primary foci might have furnished the source for aspiration with intrabronchial focal extension, has been mentioned in the discussion dealing with these two specific instances.

It seems, then, on the basis of the material presented, that in the course of primary tuberculous infection, restricted as it might remain to one or rarely more primary foci and the regional lymph nodes, additional "foci" are formed which, in their various more or less advanced involutionary stages, as found postmortem, cannot be distinguished structurally from the primary focus. We also could observe such additional foci in fairly recent stages in cases of progressive primary tuberculosis in children, formed by perifocal spread in a more or less limited radius around the core of the primary complex or by focal extension to different parts of both lungs, be it by the hematogenous route or via bronchi. In these few incidental observations there was but little or no difference in the size of the postprimary lesions and of the primary focus. That sometimes such additional foci, indistinguishable in size and structure from the primary focus, might also develop in the course of primary progressive tuberculosis of adults is shown by the postmortem findings in the following case of acute overwhelming tuberculosis of a twenty-two year old white woman (B. G. H. 5047). (Plate 11)

There were seven recent focal lesions altogether, five in the left upper lobe and two in the right subapical area. Three of these were seemingly well encapsulated, round, 3 to 4 mm. in diameter, one in the lateral field of the left upper lobe, about 3 cm. below the level of the apex, the other two in the midportion of the same lobe at the hilar level. In the left subapical area there were two additional foci, firmly caseated, close and medial to the former, surrounded by hemorrhagic zones. Finally, there were two foci, similar in structure and size, in the subapical portion of the right upper lobe, also with marked hemorrhagic zones, firmly caseated.

The lymph nodes regional to the left upper lobe, especially the upper tracheobronchial and anterior mediastinal nodes, showed many caseated pinhead- to lentil-sized conglomerate tubercles. In the lymph nodes of the left venous angle the caseation was fairly complete. There was an unusually densely seeded miliary tuberculosis in both lungs. The lymph nodes regional to the right lung and the left lower lobe contained caseated conglomerate tubercles, only slightly smaller than those in the lymph nodes on the left side. There was no tuberculosis in the lymph nodes of the right venous angle.

The other findings of acute tuberculosis included: recent hemorrhagic pleuritis around the left lower lobe; distinct hematogenous dissemination with many recent tubercles in the spleen, in the peritoneum, especially on the lower surface of the diaphragm, scattered tubercles in the liver and distinct caseation of periportal and periaortic lymph nodes; a few conglomerate tubercles in the white matter of the brain, and diffuse tuberculous meningitis. (Intestinal tract normal.)

*Microscopic report:* Only the findings of the large focal lesions in both upper lobes will be given briefly. Left subapical area: focus, appearing as the primary (A1) and two lesions in a radius of 2 cm. medial to this focus (A2 and A3) of almost the same size.

A1: Huge, caseated focus in beginning fibrous encapsulation, apparently in connection with a bronchiolus, the more granular cheesy content of which is fusing in part with the

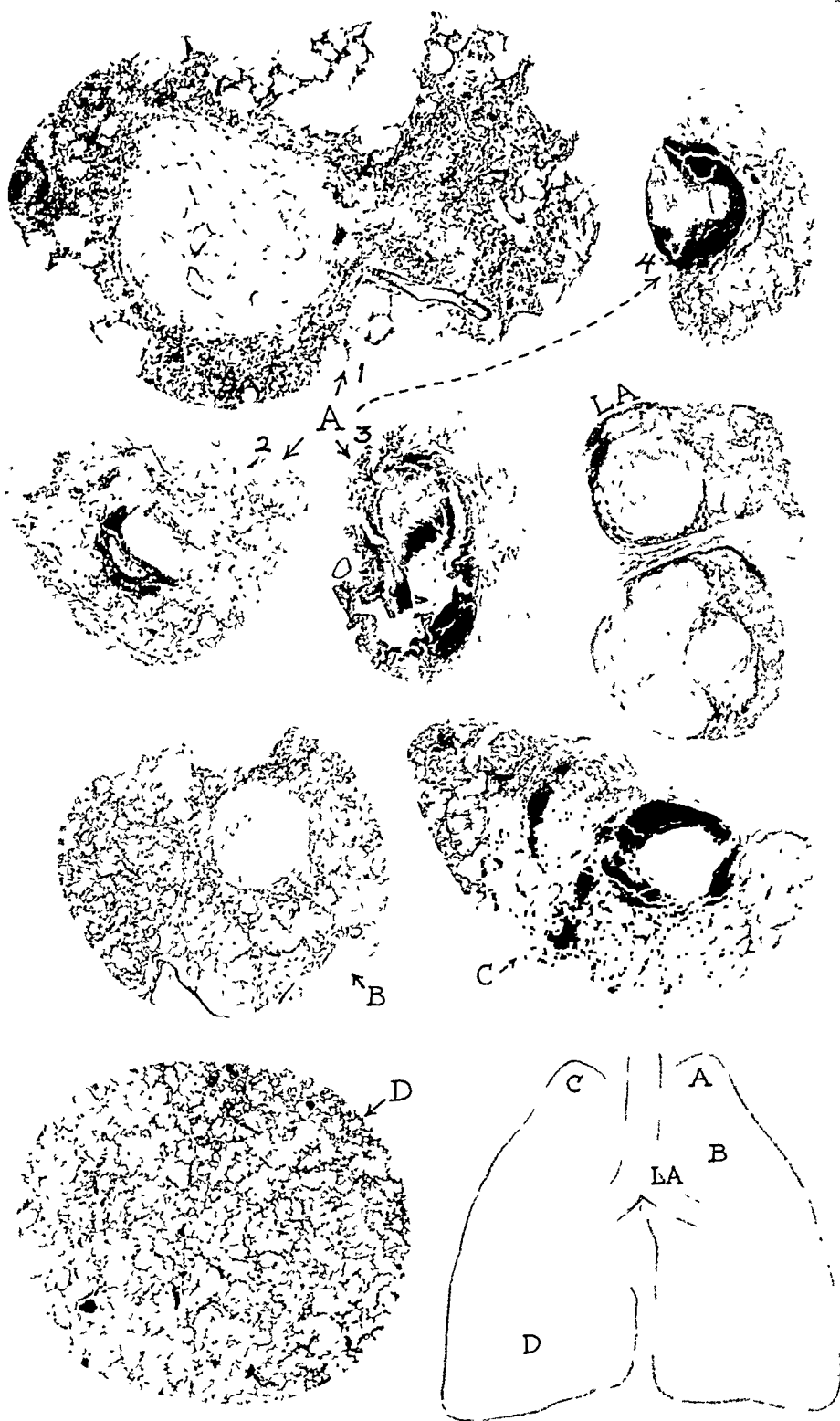


PLATE 11

compact focus. The wall of this bronchiolus is in part still preserved. The caseated alveoli are well recognizable in the elastic tissue stain, although a considerable portion of the elastic tissue appears destroyed.

A2: Huge, caseated focus, less well defined than the former. The most impressive features here are frank hemorrhages along the border and in part within the peripheral caseated areas. Contiguous to this focus are several recent caseated lesions within small bronchi, of acinous arrangement, part of their wall still recognizable.

A3: The firmly caseated central area is entirely surrounded by a hemorrhagic zone. In the elastic tissue stain this area shows massive caseation; the elastic structures in the wall of the bronchi, closely contiguous with the focus, are mostly destroyed. The blood vessels in the caseated centre are rather well preserved. This centre and, in fact, most of the caseated area appears completely undermined by recent hemorrhages. Part of the blood apparently forced its way into the softened centre which has disintegrated.

A third, somewhat smaller focal lesion (A4), surrounded by a hemorrhagic zone, was found in the same area, very similar to the lesions described (A2 and A3). In its liquefied centre some mucoid material, suggesting retained secretion within a completely caseated small bronchus or bronchiolus, could be seen.

Midportion of left upper lobe (B): The two huge tubercles show, histologically, complete, firm caseation. They are about 3 to 4 mm. wide. Their capsule is distinct, consisting of thin mesenchymal membranes. The elastic tissue in the firm caseated centre is well preserved. Both foci are of almost identical structure and size, indistinguishable from the firm caseated focus (A1) in the subapical field of the same lobe. They are not surrounded by hemorrhages. The lung tissue in very close relation to these foci shows densely seeded miliary tubercles of the same size and distribution as those seen in different parts of the lungs, especially in sections taken from the right middle and right upper lobe.

Subapical portion of right upper lobe: The two foci are firmly caseated and surrounded by a hemorrhagic zone. One of them measures 3 mm. (C), the other is only slightly smaller. The elastic tissue stain points to fairly recent caseation. These two foci are very similar in structure and with regard to the hemorrhagic reaction to the two lesions (A2 and A3) in the left subapical field. They are closely surrounded by very dense miliary and conglomerate tubercles.

The histological findings in all lymph nodes draining both lungs can be presented together, as there was, as already noted grossly, but little difference in the size of the caseated tubercles. The entire bronchomediastinal groups were examined with the angulus lymph nodes. Most of the lymphoid structure in the left upper tracheobronchial (LA) and anterior mediastinal lymph nodes was replaced by massive caseation. There was slight hyalinization of the reticulum and some fibrosis in the wall of smaller conglomerate tubercles. In the mediastinal group a few smaller epithelioid cell tubercles were surrounded by recent hemorrhages. Otherwise there were large conglomerate tubercles with central caseation. The lymph nodes in the left venous angle showed extensive caseation and many huge conglomerate tubercles with slight hyaline changes, and others in a very active state with central necrosis. A few of the lymph nodes from the left venous angle were almost entirely caseated. In the lymph nodes of the left lower tracheobronchial group there were small and few conglomerate tubercles, in part caseated. Practically identical lesions were seen in some lymph nodes of the right lower tracheobronchial group. The right upper tracheobronchial and paratracheal group showed again dense conglomerate tubercles with central necrosis and slight hyalinization of the reticulum in some of the smaller tubercles. Some of the lymph nodes within this group were almost entirely intact except for proliferation of endothelial cells but not in nodular fashion. The lymph nodes near the hilum of the right lower lobe showed huge caseated conglomerate tubercles,

almost as marked as those observed in the lymph nodes from the hilum of the left upper lobe.

Sections taken from different parts of both upper lobes, right middle lobe and both lower lobes showed fairly identical changes: Very densely seeded miliary tuberculosis, frequently with confluent tubercles, some of which penetrated into smaller bronchi and bronchioli, and with massive recent caseation of smaller bronchi in general, clearly in close relation to nearby conglomerated tubercles. There is distinct localized emphysema between these tubercles. The conglomerate tubercles are somewhat less numerous in both lower lobes (D).

The periaortic, periportal and peripancratic lymph nodes showed rather marked recent caseation. Spleen, liver, parietal peritoneum and the white matter of the brain showed all typical small conglomerate tubercles; in the brain and spleen with some central caseation; in the liver invading the walls of small bile ducts. (A most detailed histological protocol is attached to the file of this case; the reports given above are considerably condensed and summarized.)

The X-ray picture of the undissected specimen shows a typical, dense distribution of miliary tubercles and conglomerate tubercles. The tubercles appear of slightly larger size in the upper parts of both lungs. The lesion grossly suspected as the primary focus is presented by a hazy density, about 4 mm. in diameter, in the left subapical field. There is nowhere any trace of chalky or calcified changes.

*Epicrisis:* This is a typical case of recent primary tuberculosis with several focal lesions in the left upper lobe, three of these within a radius of 2 cm. in the lateral subapical field, two in the midportion of the left upper lobe, and two only slightly smaller foci in the right subapical field. There is extensive lymphogenous progression, slightly more marked in the lymph nodes regional to the left upper. The lymphogenous spread from the right lung, however, is also distinct. Only the massive caseation of the lymph nodes in the left venous angle, in connection with the lymph nodes along the innominate vein, apparently points to a direct extension from the lymph nodes draining the left upper lobe, including the anterior mediastinal group. There is a very densely seeded miliary tuberculosis with many conglomerate tubercles invading a large number of bronchioli and small order bronchi. Whether or not the firmly caseated focus in the left subapical field and the two foci in the midportion of the left upper lobe are all true primary lesions cannot be decided. Their structure and size are identical. Of particular interest is that in one of them a direct connection with a small bronchus was incidentally disclosed, in a few serial sections. The four additional firmly caseated foci—two in each subapical field—surrounded by hemorrhagic zones, which were most impressive already at dissection, might represent intrabronchial focal extension from the primary foci. Those in the left subapical field were in close topographic relation to one of the primary foci. The elastic tissue stains disclosed that these foci had apparently formed within smaller bronchi. The elastic membranes in the walls of these bronchi were for the most part destroyed by massive caseation and tuberculous granulation tissue. The extensive capillary hemorrhages surrounding these focal caseations resemble hemorrhagic zones, seen sometimes in early, rapid intra- and peribronchial progression of tuberculosis. In many sections taken through the areas with dense miliary and conglomerate tubercles,

no hemorrhages were seen. It is only for this reason that the hematogenous route appears less likely as the pathway for these hemorrhagic, huge focal lesions. On the other hand, in a picture with such extensive hematogenous seeding, it should not be ruled out entirely. The involvement of many small bronchi and bronchioli by the proliferating hematogenous miliary tubercles considerably complicates the entire picture. Many of these smaller tubercles might very well have formed following intrabronchial spread. The van Gieson stain shows the walls in all the larger foci relatively faintly stained, pointing for the entire picture to an unusually recent infection. There are especially no adhesions around either lung.

In relation to the findings, the history of this patient is of great interest. Two years previous to admission, the tuberculin test and the X-ray film were entirely negative. Admission was on the 2nd of May, 1942. Five months before this date the patient had given birth to her second child. Since this time she has lost 18 pounds, felt tired, weak and had night sweats. An X-ray film taken on admission showed a picture diagnosed as fairly uniform miliary tuberculosis in both lung fields. The patient died on the 16th of May, two weeks following admission. It is probable that even earlier clinical and X-ray examination would have pointed to a progressive miliary tuberculosis in both lungs. The few focal lesions in the upper parts of both upper lobes were too recent and too small for clinical detection.

In our attitude to the probable pathogenesis of the focal lesions presented in our anatomical material we have—with few exceptions—strongly favored the intrabronchial route as against the hematogenous. This is primarily based on the entire gross anatomical picture in the cases presented in this study, especially in comparison with the well known findings of more or less generalized miliary tuberculosis of the lungs and with the anatomically less common picture of uniformly scattered large nodular pulmonary tubercles combined with analogous findings in spleen and liver. One of our forthcoming papers on incidental findings of multiple chronic hematogenous tubercles will present—we believe—quite clearly this distinction. Although the usually marked lymph node changes, regional to the primary focus, could serve as indirect source for invasion of the blood-stream by tubercle bacilli, the small number of the additional foci, their location, their occasional arrangement close to the primary focus and especially their size and the complete absence of hematogenous tubercles, miliary or larger—all this did not seem to point to the circulating blood as the more likely pathway.

That the decision, whether or not tubercles formed in the lungs are hematogenous, is in general rather difficult, is clearly stated by Loeschke (17) in a general review on hematogenous tuberculosis. It is easy in distinct uniform miliary seeding to all parts of both lungs combined with miliary tuberculosis in the systemic circulation. On the other hand, miliary lesions can also be formed in bronchogenic dissemination. Their histological picture, showing such acinous productive tubercles, might be indistinguishable from hematogenous foci established in miliary tuberculosis.

In hematogenous tuberculosis, according to Loeschke, larger infarct-like foci develop only if an arterial branch has been affected by tuberculosis. This is a very rare occurrence. Except for the true caseated infarct, larger hematogenous tubercles are not seen even in typical miliary tuberculosis. Only the uniform seeding in both lungs points, in the opinion of Loeschke, to the hematogenous route. Unilateral foci, or foci restricted to one lobe, should "primarily" not be considered of hematogenous but rather of bronchogenic origin.

Our analysis of the lesions on focal extension and the conclusions arrived at are in agreement with those views of Loeschke, expressed in reference to apical foci, including the so-called Simon foci and their alleged hematogenous nature. This will be evident also from our discussion of the pathogenesis of the true apical and subapical reinfect in one of the following papers.

As in some other problems in human pathology in which direct observation is impossible, it is the weight of facts, based on experience such as can be gained only in careful work in the dissecting room, in cases of tuberculosis as in other infectious diseases with embolic phenomena, which alone can guide one in the approach to pathogenetic problems, as presented in this paper.

#### SUMMARY

This study is based on detailed morphological analysis of tuberculous lesions in 6 children and 49 adults, including 3 cases of progressive primary tuberculosis in children and one case of active primary tuberculosis in an adult. In the remaining 45 cases with various causes of death, the tuberculous lesions were incidentally observed, postmortem. In all of them, one or more additional focal lesions, apart from the primary complex, were found with the same histological structure and of either the same or only slightly smaller size as the primary focus. These additional lesions, whose postprimary character was clear because the regional complex change was missing, were located in various parts of both lungs, including the upper (subapical and apical) portions of the upper lobes. Their distribution is indicated in tables 1 and 2. When two or more of such foci were seen scattered over the entire area tributary to the tuberculous lymph nodes forming the primary complex, especially when arranged within a closer radius, it was impossible to identify a single focus as the primary. Anatomical and topographical analysis of these lesions, especially of those found in a relatively recent state, suggests intrabronchial spread from one or more primary lesions in their early active phase as one important pathway. Grossly masked penetration from tuberculous hilar lymph nodes through the wall of the bronchus into the bronchial mucosa can also lead to focal lesions of primary focus character. In the majority of the cases studied there was no evidence of hematogenous tuberculosis. In the very few cases in which these additional foci were seen together with hematogenous metastases in spleen, liver or kidneys, or with typical miliary tubercles scattered over both lungs, their huge size and their close relationship to small order bronchi, the oblong shape and occasional evidence of central cavitation made it difficult to disregard the bronchi as the probable pathway, in spite of a clearly present hematogenous spread. The

formation of these focal lesions, usually few in numbers, of primary focus size and structure is referred to as focal extension. Only in cases of active tuberculosis, especially of the gradually progressing (protractive) type, huge single focal lesions might form by focal hematogenous extension preceding the generalized miliary dissemination. Focal superinfection during the relatively recent phase of the primary complex can also conceivably lead to these additional single foci of primary focus character. In the majority of our observations of the primary focus and the additional foci in a uniform obsolete state, no arbitrary decision favoring either focal extension or superinfection can be made. The literature referring to similar observations of "multiple primary foci" is discussed.

The histological structure, alone, of recent stages as well as in the advanced states of involution is neither an exclusive diagnostic criterion of the true primary focus nor indicative of a specific pathogenesis of the postprimary additional foci discussed in this paper. Focal extension by intrabronchial or by hematogenous spread as well as focal superinfections, which always are single intrabronchial aspirations, can lead to postprimary foci of identical structure and similar size with the primary focus. Nor is the structure of an obsolete calcified hematogenous miliary tubercle necessarily different from that of a primary focus. Such a miliary tubercle is, as a rule, only of considerably smaller size.

#### SUMARIO

Básase este estudio en un minucioso análisis morfológico de las lesiones tuberculosas en 6 niños y 49 adultos, incluso 3 casos de tuberculosis primaria evolutiva en niños y un caso de tuberculosis primaria activa en un adulto. En los otros 45 casos que reconocían varias causas de muerte, las lesiones tuberculosas fueron observadas fortuitamente en la autopsia. En todos ellos se descubrieron una o más lesiones focales, aparte del complejo primario, que mostraban la misma composición histológica y tamaño idéntico o sólo poco más pequeño que el foco primario. Otras lesiones cuya naturaleza postprimaria era manifiesta por faltar la alteración correspondiente al complejo regional, estaban situadas en varias partes de ambos pulmones, incluso las porciones superiores (subapical y apical) de los lóbulos superiores, indicándose su distribución en las tablas 1 y 2. Cuando se observaban dos o más de esos focos esparcidos por toda la zona tributaria de los ganglios linfáticos tuberculosos que formaban el complejo primario y en particular cuando abarcaban un radio más pequeño resultó imposible identificar ningún foco aislado como primario. El análisis anatómico y topográfico de dichas lesiones y en particular de las encontradas en una etapa relativamente reciente indica que una vía importante es la propagación intrabronquial desde una o más lesiones primarias en su fase activa temprana. La penetración más o menos enmascarada desde los ganglios linfáticos tuberculosos del hilio a través de la pared del bronquio a la mucosa bronquial, también puede producir lesiones focales de naturaleza de foco primario. En la mayoría de los casos estudiados no había signos de tuberculosis hematógena. En los poquísimos casos en que se observaron esos otros focos junto con metástasis hematógenas en el bazo, hígado o riñón o con típicostubér-



culos miliares esparcidos en ambos pulmones, su enorme tamaño e íntima relación con los bronquios más pequeños, la forma oblonga y signos ocasionales de cavitación central apenas permiten desatender los bronquios como vía probable de difusión a pesar de existir claramente propagación hematógena. La formación de esas lesiones focales, por lo general escasas, de tamaño y estructura primarios, lleva el nombre de extensión focal. Sólo en los casos de tuberculosis activa y en particular del tipo de evolución gradual (prolongada) las enormes lesiones focales aisladas podrían ser formadas por difusión hematógena focal que precediera la diseminación miliar generalizada. La superinfección focal durante la fase relativamente reciente del complejo primario también podría, posiblemente, dar origen a esos otros focos aislados que muestran la naturaleza de los focos primarios. En la mayoría de nuestras observaciones del foco primario y de los otros focos en estado anticuado uniforme no cabe ninguna decisión arbitraria en pro ya de la extensión focal o de la superinfección. Discútese aquí, de paso, la literatura relativa a observaciones semejantes de "focos primarios múltiples".

La histología, tanto en las fases recientes como en las avanzadas de la involución, no dicta por sí sola una pauta diagnóstica exclusiva del verdadero foco primario ni indica una patogenia específica para los otros focos postprimarios discutidos en este trabajo. La difusión focal por medio de la propagación intrabronquial o hematógena así como de superinfecciones focales, que son siempre aspiraciones intrabronquiales aisladas, puede dar origen a focos postprimarios de estructura idéntica y tamaño semejante a los del foco primario. Tampoco es la estructura de un tubérculo miliar hematógeno calcificado vetusto forzosamente distinta de la de un foco primario; aunque su tamaño es por regla general mucho menor.

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# ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS<sup>1</sup>

## XIV. Tuberculous Lesions in the Apical and Subapical Field in Connection with Primary Tuberculosis

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Our interest in tuberculous lesions restricted to one apical or subapical area, with corresponding changes in the regional lymph nodes, was aroused for the first time by an incidental postmortem finding (case 2645, 1934). From the roentgenogram and on the basis of the anatomical and histological analysis, the conclusion appeared justified that the pulmonary lesions in this case represented a healing state of a primary tuberculous infection of very striking "infraclavicular" localization (this case is the first to be discussed in a series of 8). Later on, in the course of our studies, a few similar anatomical observations were made, including a few cases of progressive tuberculosis, in which the question of the primary nature of these apical and subapical lesions appeared as the foremost problem in their morphological analysis.

Before presenting our findings in some detail relative to the pathogenetic concept, as indicated in the title of this paper, it might be of interest to recall the views held by many investigators—clinicians and pathologists—on the nature of the tuberculous lesions in the upper parts of the upper lobes, which frequently seem to initiate progressive pulmonary tuberculosis. These apical and subapical lesions were, in general, not looked upon as the result of a primary infection. Whether or not the anatomical facts, as revealed at postmortem, were always unequivocal as to the postprimary nature of these lesions cannot be stated with complete assurance. Extensive pulmonary lesions, especially in the presence of several cavities, with the topographic relation between the components of the primary complex obscured, or with no clear evidence at all of a lesion which could be designated as the primary focus, present great obstacles to pathogenetic analysis on morphological grounds alone, especially in the more chronic state of such lesions, as seen in many cases of pulmonary tuberculosis in the adult. The impression one gains, however, from carefully controlled studies—to mention especially those of Schuermann (1)—is that, in the material examined in two large German cities (Hamburg and Dresden), pulmonary tuberculosis was the result of postprimary infections and followed apparently to a considerable extent true (exogenous) superinfection or reinfection. These observations were made at a time, in the years following the World War, when effects of a typical primary infection were demonstrable in about 90 per cent of children and young adults below eighteen years of age in Schuermann's material. In other large cities of the European continent, especially in Germany, the percentage of typical findings of a primary complex varied between 55 and 80 to 90 per cent in the same age group. It might be

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assumed that the type of this material studied in different pathological institutes, which was obtained from a population with a high index of tuberculous infection established in childhood or early adult life, had presented little, if any, occasion to question the postprimary character of the early apical and subapical tuberculous lesions at that time. Until quite recently the discussion—with many an argument—revolved entirely about the pathogenesis of these postprimary apical or subapical lesions, especially as to their relation to the primary complex. The contending views were exogenous superinfection or true reinfection *vs.* hematogenous metastases from the components of the primary complex.

Also, the term “reinfection type,” applied to these lesions, indicates that they are not considered the direct result of a primary tuberculous infection, regardless of the pathogenesis of this so-called reinfection. In the strict anatomical sense, this term stresses a different picture, clinical and anatomical, as compared with the usually focally arranged primary pulmonary infection with formation of the primary complex.

In the last fifteen years our views as to the time of the first infection with demonstrable effects of an acquired sensitivity to tuberculin have considerably changed, as is generally known. On the basis of large scale tuberculin testing of children and young adults, including the high school and college groups, it appears as a fair conclusion that first tuberculous infection was, in the majority of these observations, not acquired during childhood. A distinct decrease in the number of tuberculin-positive children has been reported also from a few European countries. In Germany, according to Redeker (2), the number of positive reactors among children below fifteen years of age had dropped from about 70 per cent in the years following the World War to 30 to 40 per cent in 1937. In addition, it has been learned in the course of systematic tuberculin testing that a considerable number of negative reactors among children and young adults show roentgenological evidence of calcification which, in the majority of these cases, can be taken as representative of a calcified tuberculous scar in the pulmonary parenchyma or in the lymph nodes, or in both. Such a discrepancy between positive X-ray findings and negative tuberculin tests until quite recently was hardly known, although this fact could be explained merely by the lack of comparable investigations carried out on some similar scale in the past. Only a few of these discrepancies need to be mentioned here; more are known, and many more most probably will be published from different sources, provided such examinations are continued.

Crimm and Short (3) found, among 384 cases of children and young adults between one and twenty years of age, 191 with X-ray evidence of pulmonary calcification with a negative tuberculin reaction. Of these, 4 developed later a sensitivity to tuberculin, indicating—in the opinion of Crimm and Short—a reinfection, while 14 lost the sensitivity to tuberculin in a period of four years following their last positive reaction.

Tortone, Chattas, Myers, Stewart and Streukness (4) reported in a follow-up study of 4,328 children under six years of age, 16.4 per cent of which had a

positive tuberculin reaction, that 22 of these lost their sensitivity to tuberculin and remained negative to repeated intracutaneous injections of 1 mm. of Old Tuberculin. Similar observations were published by Stewart (33) and by Gass, Murphy, Harrison, Puffer and Williams (34) on children, and by Baker and Holoubek (35) on medical students. Oekomonopolos (5) found among 13 negatively reacting children between nine and twelve years of age, from a rather poor hygienic environment, 8 with positive X-ray findings, pointing to calcified tuberculous lesions, in spite of repeated negative tuberculin reaction.

In a recent paper by Alt, Barth and Day (6), dealing with tuberculosis in medical students, 27 among 94 freshmen showed a negative tuberculin test with X-ray findings of calcareous deposits in the lungs or tracheobronchial lymph nodes. The percentage of reactors to tuberculin in five classes increased from 66.2 per cent in the first year to 93.4 per cent in the fourth year. As figures on previous tuberculin tests before the college age is reached are, in many instances, not available at the present time, it cannot be stated with certainty how many of these additional reactors actually acquired their first infection while in medical school. Probably, in the majority of these cases, the turn from the negative to the positive reaction did indicate the primary infection.

In a previous paper (no. I) (7), attention was called to the incidental post-mortem findings of calcified primary foci in children known to have been negative to tuberculin while observed in the hospital. Two such cases were reported a few years ago. In both of them a typical healed primary focus was found in the lungs. The infection in these cases had not spread to the regional lymph nodes, which were entirely free of scars from tuberculosis, as proved by complete serial sections. There is, however, still very little, if any, additional anatomical evidence available at present to substantiate on a more reliable, morphological basis the considerable incidence of such discrepancies in the tuberculin reactions and positive roentgenological evidence of calcified scars presumably of tuberculous origin.

That in the last ten years little support has been given by morphologists to this entire question of the incidence of tuberculous lesions in children and young adults is as regrettable as it is surprising. It would be of great interest to have comparable figures from different cities, especially on the incidence of tuberculous lesions in older children and young adults from fifteen to thirty years of age. Such figures could carry some information of immunobiological significance, if amplified by the results of the tuberculin reactions. It has been stressed in one of the preceding papers that in any morphological study of tuberculosis the method employed cannot be thorough enough, and it was especially emphasized that it should not only include X-ray photographs of the undissected specimens, especially of the lungs, the tracheobronchial tree and the bronchomediastinal lymph nodes, but also most detailed dissection and complete histological control of the different lesions found, especially of all calcified nodules or structures. Landé and Wolff (8), in a recent article on the frequency of tuberculous lesions at autopsies, complained of the paucity of data from postmortem material. They not only missed the data reported on children and adults (papers II (9)

and VI (10)), but also the method described for such investigations. The lack of X-ray control in their examinations raises some doubt as to the correctness of their findings.

Not much reliance should be placed on the claim of Carnes, made in a recent paper on the present incidence of tuberculous infection (11), that the small bony particles within alveolar spaces, formed by metaplasia, are usually easy to distinguish grossly from ossified tubercles. Histological study of the smallest lesions appearing as distinct shadow-giving structures on the roentgenogram taken postmortem is as essential for reliable data on the incidence of tuberculous lesions as the necessity for great patience and care in finding them in the gross specimens and not missing them in the paraffin blocks. Contrary to the statement of Carnes, these minute metaplastic bony particles and also phleboliths are by no means uncommon findings in the lungs. This will be shown in one of the following papers dealing specifically with these and other calcified and ossified structures of nontuberculous origin. It was stated clearly in the introduction to my paper on the incidence and anatomical types of tuberculosis in children (9) that "conclusive evidence of the incidence of tuberculosis among children and adults rests entirely on careful postmortem work," also that "figures obtained with tuberculin testing in children and young adults do not necessarily indicate exactly the number of those harboring lesions due to infection with tubercle bacilli." To this, Carnes has made no reference. It is even more to be regretted that some results of our studies, especially those dealing with the incidence of tuberculous lesions in adults, were apparently not read at all by Carnes. I cannot find any other reason for the statement by Carnes, in discussing my findings on the incidence of tuberculosis in children: "the incidence of lesions in adults dying of other diseases is not calculable from his data." The complete data in absolute numbers and percentages are given in tables 1 and 2, page 88 (10).

This deviation from the principal discussion of our topic on apparently primary lesions in the apical and subapical area should serve only one purpose: to stress the fundamental importance of most careful anatomical examinations, especially in dealing with the young adult groups in the late teens and in the third and fourth decade of life. If this is carried out, especially in all those instances in which tuberculosis is not the cause of death, a fairly complete anatomical analysis can be accomplished.

The interest in the pathogenesis of tuberculosis in the young adult has been stimulated anew primarily by clinical studies in the last ten years. Very careful observations have been reported which seem to suggest the great possibility that primary tuberculosis in the young adult can present itself directly as a distinct tuberculous infiltration in or near the apex with no recognizable relation to an associated or preceding primary complex. Of such clinical studies, on the pathogenesis of the early or incipient tuberculosis, the work of Malmros and Hedvall (12) should be mentioned first. Of 3,336 students and nurses, among whom all negative reactors were retested at least once a year and radiographically examined at short intervals, 133 cases of active tuberculosis were detected.

As in 47 of these students the tuberculin reaction had been negative and the radiogram normal—when first examined after entering the college—the change to a positive reaction followed by a positive X-ray finding was considered the result of the primary tuberculous infection. In 19 out of these 47 cases, distinct clinical signs of early pulmonary tuberculosis were observed: minute or small cloudy spots, in a few cases with infiltration-like pictures with mottled foci, all changes usually within the supraclavicular region. In no one of these cases was there any evidence of hematogenous dissemination. In 14 out of these 19 cases, no primary focus could be demonstrated by X-ray. In the remaining 5 cases, these supraclavicular pulmonary lesions were preceded by roentgenological evidence of a primary focus or by erythema nodosum. In 104 additional cases the formerly negative tuberculin reaction changed into a positive one, but no lesion could be demonstrated, neither by X-ray nor clinically. The interval between the appearance of demonstrable apical lesions and the last negative tuberculin reaction was eleven and one-half months. In the 5 cases in which erythema nodosum or a demonstrable primary lesions had preceded the initial changes in the supraclavicular area, there was an interval of ten months between the appearance of the primary lesion and the manifestation of the supraclavicular lesions. These clinically demonstrable foci are called "subprimary initial foci." Malmros and Hedvall stress, in contradistinction to the early infiltration of Simon and Redeker, that the location of these lesions points more to the apical area or to the first intercostal space rather than to the subclavicular area. They feel that these initial foci seem to correspond to the so-called apical foci of Simon which were believed to be effects of an early hematogenous spread from the primary complex. Malmros and Hedvall, in using the name "initial foci," indicate that their opinion of the significance of these lesions is different from that of Simon. They do not state definitely, however, whether these foci are the result of intrabronchial or of hematogenous spread. It is felt that only postmortem examination of such cases which showed radiologically these early lesions could solve their pathogenesis.

In another paper published at the same time, Malmros and Hedvall (13) state that the most common clinical manifestation of primary tuberculous infection in college students and nurses is the X-ray evidence of a primary focus. It was present in 21 out of 47 cases.

Wallgren (14), in a recent paper on primary tuberculous infections in young adult life and in children, in referring to the papers of Malmros and Hedvall, does not seem to share their view that these cases actually represent the first stage of pulmonary tuberculosis from a first infection. On the other hand, he believes that pulmonary tuberculosis probably develops more readily from a fresh, active primary complex in the lung acquired during the age of predilection to phthisis, than from an old childhood infection.

If we try to correlate these two views, it seems that a recent primary complex might be present also in those cases of Malmros and Hedvall in which no clinical or X-ray evidence of it can be demonstrated, provided, of course, that the primary character of the tuberculous infection is unquestionable.

Stiehm (15), in reviewing a five-year tuberculosis program among 15,000 University of Wisconsin students, came to the conclusion that progressive tuberculosis may develop from the first infection. He based this on the experience that more tuberculosis was observed among nurses previously not infected, than in the group which was already tuberculin-positive at the beginning of their training. In his series, in 4 cases the development of cavitations from lesions of first infection was observed, although only a relatively small percentage of the total infected group developed progressive tuberculosis from their seemingly first contact with tubercle bacilli. The incidence of positive reactors in this age group of young adults between seventeen and twenty-six years was comparatively low, varying from 22.4 to 27.8 per cent. Clinical evidence of parenchymatous lesions was observed in greater numbers among those students who did not show calcification on the X-ray film. Of 71 with active pulmonary tuberculosis, only 12 showed X-ray evidence of calcification in the lungs or at the hilum, but only in 8 of these this calcification appeared separate and distinct from the parenchymal lesions. Stiehm (15), in discussing his observations, did not feel justified to designate the parenchymatous lesions clearly as primary or as the effects of a reinfection. From the X-ray appearance alone, without the knowledge of the tuberculin tests in the past (before entrance into the college), such a diagnosis could not be made with any degree of accuracy.

Israel and Long (16), in a clinical study, found that primary tuberculosis similar in anatomical and clinical character to the typical primary types as observed in childhood is not uncommon in adolescents and young adults. The variety of types observed did not permit an accurate diagnosis of the lesions seen relative to the question of a real primary or of a reinfection type on the basis of the roentgenological appearance or the clinical behavior. In their opinion, differentiation of tuberculous lesions in a primary and reinfection type can be established so infrequently in clinical examination, that the practical importance of this distinction appears questionable.

It is highly illuminating that Ghon and Roman (17 and 18), in their studies on primary tuberculosis in children, came to the following conclusions: "On the basis of anatomic considerations, we should expect all transitional types between cases with typical progressive pulmonary tuberculosis (phthisis) in the presence of an old primary complex and cases of phthisis in which a complex is missing and the progressive tuberculosis developed directly out of the primary lesion, or where a very massive infection primarily had led to the picture of phthisis." Obviously, Ghon and Roman are referring to such a type in which the primary focus has initiated the gradual development of pulmonary tuberculosis by contiguous spread and further extension via bronchi. To the pathologist experienced in the acute progressive types of tuberculosis in children and young adults, which have been observed especially in the colored population, it is well known that a massive infection right from the beginning might lead to rapid disintegration and cavitation with progressive intrabronchial spread and actual consumption. We have presented such cases in our material dealing with active progressive tuberculosis in children (paper II (9)). This acute

overwhelming infection with cavity formation and rapid progression with fatal outcome was also seen not infrequently in white infants or small children by Ghon and his coworkers. It is well recognized by pediatricians. In some of them the involvement of lymph nodes was just as marked as in typical complexes with a single primary focus.

To prevent any misunderstanding as to the nature of the lesions which will be presented in this paper, it should be stated that they have, in our opinion, no relation to the so-called Simon's foci, which Huebschmann (19) believed to be of hematogenous nature. Loeschke (20) saw these localized apical foci in children only in such cases in which the primary focus was in communication with a bronchus and, in addition, a few single foci were present close to the primary lesion. They are, in his opinion, not of hematogenous nature; nor has any proof been presented that they have any relation to the apical tuberculosis of the adult. They either heal, according to Loeschke, or lead to progressive tuberculosis in the child. In the absence of any anatomical sign of activity within the primary complex, Loeschke felt that apical tuberculosis in the youth and the adult is usually the result of (exogenous) reinfection.

The claim of Anders (21), that histological examination can prove the hematogenous nature of postprimary apical tuberculous foci in childhood, cannot be accepted in general, and particularly not for his own case in which the source for this assumed hematogenous seeding was admittedly obscured. There was no recent tuberculosis in the lymph nodes of the primary complex. In fact, from the anatomical report given, a hematogenous source can be ruled out. Although the primary lesion was not found, there were three very small calcified and ossified tubercles in the left bronchopulmonary lymph node group regional to the lower lobe. Here, then, was a recent reinfection affecting both apices, of the productive acinous type which—significantly—had caused tuberculous meningitis.

In the discussion of the pathogenesis of these apical lesions, one most valuable report of Ghon (22), in his original monograph on the primary pulmonary focus in childhood tuberculosis, has been overlooked. In case 552, that of a four year old girl, symmetrical, pea-sized, caseated nodules were found with central disintegration and recent tuberculosis of the pharyngeal tonsil and the ileum, in the presence of a calcified lesion in the right middle lobe and chalky and caseated changes in the regional bronchopulmonary and tracheobronchial lymph nodes. It is expressively stated by Ghon that there were no tubercles found in organs which could have been reached only by the blood-stream. In this case the cause of death was a brain abscess. Ghon did not specifically discuss the pathogenesis in this case which, from the anatomical facts given, could be explained on the basis of an (exogenous) superinfection. A similar observation was presented in one of the cases included in our series on active tuberculosis in children ((9), case 29, pages 30 and 32). In this case, in addition to a caseated complex with a hazelnut-sized cheesy focus near the base of the left lower lobe, recent tuberculous bronchopneumonia was found localized to the upper third of the left upper lobe. The anatomical picture was suggestive of



early intrabronchial extension from the primary focus, or of superinfection in the early phase of the primary infection. This was an entirely incidental finding in a child who died following radical mastoid operation for purulent otitis, with clinical signs of recent meningitis. The head was not dissected, but no signs of hematogenous dissemination were found in any organ.

According to Blumenberg (23), the most common type of tuberculosis in the prepuberty and puberty age is chronic pulmonary disease of the same type as seen in adults, with only small tubercles in the lymph nodes. Previously healed tuberculosis is considered very rare in these cases by Blumenberg, and has no effect upon the course of the tuberculous infection around the age of puberty. With this view Beitzke evidently did not agree. Beitzke (24), in discussing a paper of Schminke on morphogenetic factors in the course of human primary tuberculosis, felt it is misleading to claim that in an adult the primary infection is directly changing into a chronic tuberculosis localized in the upper parts of one or both upper lobes. According to Wurm (25), however, primary pulmonary infection in the adult could possibly lead to the formation of a primary complex, and in a relatively short time in contiguity with the focus, a phthisis might directly evolve as part of this first infection. The so-called puberty phthises of Aschoff might possibly belong to this group.

Opie (26), in a paper entitled *Present Concepts of Tuberculous Infection and Disease*, states that tuberculosis of first infection in adolescence and adult life affects the apices with increasing frequency. White persons first exposed to tuberculosis after the fifteenth year of age develop, according to Opie, tuberculosis of the adult type with few exceptions. He admits that relation of the first infection to this adult type is still under discussion and for this reason is against designation of the latter as reinfection type. If the so-called adult type was observed in the presence of calcified nodules pointing to first infection, it was only in persons with continued contact with a tuberculous source. I do not know how far these statements of Opie were corroborated by morphological postmortem examination.

How much we could have learned from carefully analyzed postmortem observations is evident from a recent paper of Kettelkamp and Stanbro (27) on tuberculosis in identical twins. In this report, so important in regard to inherited constitutional factors, it is most regrettable that the postmortem examination, as given, does not reveal clearly the type of tuberculous infection—whether or not this progressive tuberculosis showed the anatomical criteria of first infection, of superinfection or of true reinfection. Also, in Sweany's paper entitled *The Pathology of Primary Tuberculous Infection in the Adult* (28), the brief data given on the postmortem findings in 19 cases (3 others were only clinical observations) are too incomplete and, therefore, inadequate for accepting the author's interpretation as anatomically sufficiently proved. Sweany states, on the basis of this material, that adult primary infection seems to assume the proportions of the reinfection type. For any discussion of the pathogenesis of tuberculosis in general and of the apical and subapical lesions in the young adult in particular, most complete anatomical reports are indis-

pensable. Sweany admits that in many of his cases the question might be raised as to their primary character. He adds that previous infections might have been entirely resorbed, too small to leave a residue. However this might be, at the present state of our knowledge of human tuberculosis it is most unlikely that in *young* adults residues should be resorbed completely. Opie, too, in the discussion of the relationship between the lesions of first infection and those of the adult type, such as presented by Sweany, felt that they would receive varied interpretations from pathologists.

Finally, a brief reference should be made to the symposium on *The Primary Tuberculous Infection of the Adolescent and Adult* at the occasion of the 10th Conference of the International Union against Tuberculosis, in Lisbon in 1937. Scheel (29) and Burrell (30) both stated that first infection of the adult does not have a different character from that usually observed in children. While, according to Burrell, it may lead to fibrocaseous tuberculosis, this (so-called adult) type is most frequently regarded as a reinfection of a tuberculin reactor, which might follow directly the first infection. Likewise, Redeker (2) felt that chronic phthisis, initiated directly by the primary tuberculous infection of an adult, is only rarely seen, whereas superinfection or hematogenous metastases are usually responsible for the change of a first infection into progressive tuberculosis. According to Plunkett (31), there are few reliable data available to prove that primary tuberculosis presents a different pathological or clinical picture in the young adult as compared with that seen in children. This stand is based on a quotation of Pinner that too few studies on the pathology of primary infections in adults have been made so far. Also quoted by Plunkett are postmortem findings on adult Negroes of Jamaica, by Opie. In these, one or both apices were the site of the first infection, which was accompanied by caseation of the adjacent lymph nodes. Further included in this discussion were the findings in 44 colored and 21 white adults, as given by Everett. While of 44 American Negroes, one-half showed the usual primary type and the other half the character of the adult type, in the 21 instances of pulmonary tuberculosis in white Americans, the adult type was present in all except 2. Whether or not the primary character in these (adult) types was proved anatomically beyond any doubt, cannot be learned from the quotations.

It appears, then, from the report of the symposium on primary tuberculous infection of the adolescent and adult, that no sufficiently complete morphological data have become known to prove that the anatomical picture of first infection is different in its extent and effects from the usual primary infection in other age groups. The only conclusion which can be drawn, based especially on Opie's findings on adult Negroes, is that the primary focus is more often localized in the apical area in the young adult group than in children.

From the foregoing notes on the literature, it is obvious how justified the request for carefully controlled postmortem examination is in any case in which all clinical evidence seems to point to primary tuberculosis lesions in the apical or subapical area, with several scattered lesions or with more substantial infiltration. Such findings, in the majority of cases, are apt to be entirely incidental,

as they in themselves cause death only if they lead to rapid intrabronchial progression or to progressive hematogenous seeding, with or without tuberculous meningitis. The number of cases with apical or subapical lesions of first infection proved by anatomical and histological control is apparently very small.

TABLE 1

*Anatomical findings in 9 cases with tuberculous lesions in the apical and subapical areas in connection with primary tuberculosis*

CASE NUMBER	AGE RACE SEX	CAUSE OF DEATH	EXTENT OF PRIMARY INFECTION	REGIONAL LYMPH NODES	ADDITIONAL FINDINGS
GROUP I					
2645	34 White F	Diffuse purulent peritonitis	Left subapical field, about 5 cm. below apex. Several calcified, chalky-fibrous nodular lesions	Extensive chalky-caseated changes in 2 regional groups	None
3375	59 White F	Carcinoma of gall-bladder	Three ossified-calcified nodules in right subapical field, 4 cm. below apex	A few minute splinters in right bronchopulmonary, and moderate calcification in right upper tracheobronchial lymph nodes	Localized fibrocaceous re-infection in the same area slightly below the calcified lesions. No recent changes in lymph nodes
2178	34 Colored M	Carbon monoxide poisoning	Several calcified and partly ossified small foci in a cherry-sized area, right subapical field, middle third of of the lobe	Distinct calcification of one regional bronchopulmonary lymph node	None
4074	42 White F	Lymphatic leukemia	Several firmly calcified small nodules in entire left subapical field, completely calcified and partly ossified	Neither grossly nor on X-ray tuberculosis in regional lymph nodes (no histological control)	Fibrous-chalky reinfection complex with small single focus in left lower, and hyaline-caseated conglomerate tubercles in two regional bronchopulmonary lymph nodes at the hilus of this lobe. Additional single caseated focus in right middle lobe. Few recent tubercles in liver
GROUP II					
2056	44 White F	Tuberculous meningitis	Several ossified-calcified small nodular tubercles in left subapical field. Also a few calcified hyaline tubercles in the right subapical field	Minute calcified splinters in one regional left bronchopulmonary lymph node	Diffuse caseated tuberculosis of tubes and endometrium. Scattered small fibro-caseated tubercles occluding small bronchioli in both lungs, and recent localized hemorrhagic tuberculous pneumonia in right middle lobe. Miliary tubercles in liver, spleen, kidneys and myocardium. Tuberculous meningitis

TABLE 1—Continued

CASE NUMBER	AGE RACE SEX	CAUSE OF DEATH	EXTENT OF PRIMARY INFECTION	REGIONAL LYMPH NODES	ADDITIONAL FINDINGS
GROUP II—Continued					
5308	42 Colored F	Miliary tuberculosis	Several fibrocased lesions in right upper lobe close to apex, with firm adhesions to parietal pleura	Marked anthracotic induration of right upper tracheobronchial lymph nodes. (Histological: A few small hyaline conglomerate tubercles)	Cased osteomyelitis of lumbar spine, and dense miliary tuberculosis in lungs, liver, spleen and kidneys. Recent epithelioid cell tubercles in bronchomediastinal lymph nodes regional to both lungs
3981	18 White M	Tuberculous meningitis	Primary cased focus with minimal chalky changes in lower third of right upper lobe. Massive cased tuberculosis of entire subapical portion of left upper lobe, extending slightly to apices of both lower and to right subapical field. Slight lymphogenous progression on left side	Extensive caseation with soft chalky changes in regional bronchopulmonary and upper tracheobronchial lymph nodes	Tuberculoma of the cerebellum. Tuberculous meningitis
4204	36 White F	Tuberculous meningitis	Chalky-calcified primary focus upper third left upper lobe. Several chalky-calcified tubercles in both subapical fields	Localized chalky-calcified tuberculosis of one regional left bronchopulmonary lymph node	Progressive hematogenous tuberculosis, including tuberculous caries of first left rib, cased tuberculosis of splenic, peripancreatic, periaortic lymph nodes, and thoracic duct. Tuberculous meningitis
3462	22 White F (no histological control)	Pulmonary tuberculosis	Several calcified small tubercles in left subapical area	Minute calcified splinters in a few bronchopulmonary and left upper tracheobronchial lymph nodes	Extensive fibrocaceous tuberculosis with huge cavity in left upper lobe, and massive intrabronchial spread through both lungs, especially to the right

It is for this reason that we wish to present anatomical observations made in 4 cases in which later stages of tuberculosis were found incidentally, postmortem (group I). Although in all, these lesions had reached an advanced state of regression, their topographic and structural relationship, including the tuberculous changes in the regional lymph nodes, seemed to point to a primarily locally spreading first infection in the subapical or apical area. To these incidental findings from cases in which the cause of death was not tuberculosis, the reports on 5 cases of active, fatal tuberculosis will be added (group II).

In the first of these from group II, the apical and subapical lesions in connection with the primary infection were in obsolete state (similar to case 4), apparently representing the original source for a chronic, gradually progressing hematogenous tuberculosis, terminating in tuberculous meningitis. In the

second case, the clinical history of which was fairly well known, the complete anatomical and histological analysis clearly pointed to a primary, locally infiltrating apical lesion with but minimal spread to the regional lymph nodes and with distinct hematogenous tuberculosis to the spine. From this, in turn, a recent overwhelming miliary seeding had originated. In the third case, the anatomical findings seemed to point to a massive superinfection in the subapical and apical area, especially in the left lung, in the presence of a typical primary complex still in active state with but minimal chalky changes and very extensive caseation. As the primary focus was located close to the subapical area of the right upper lobe, it is obvious that the pulmonary lesions—as found in this case—could have been easily mistaken in any clinical examination for a primary tuberculous infiltration of the apical and subapical area. The cause of death was tuberculous meningitis preceded by a tuberculoma of the cerebellum. The findings in the fourth case were somewhat similar to case 3. Primary focus and additional lesions in the subapical and apical area were in close topographic relation to each other. The histological analysis in particular showed no structural difference of all these lesions. They appeared in a somewhat more advanced state of caseated chalky regression. Whether the typical apical and subapical lesions were caused by superinfection during the early primary phase or by focal intrabronchial aspiration from this relatively huge primary lesion located above the hilum level in the same upper lobe, could not be decided. The tuberculous lesions in the left upper lobe had led to protracted hematogenous tuberculosis involving different organ systems and ending, too, in tuberculous meningitis.

To these 4 cases of fatal tuberculosis we wish to add a brief report on the roentgenological and gross anatomical findings in another case, that of a young white woman, the last of this series. Again, there were several older calcified lesions in one apical area and relatively slight stony changes in the regional lymph nodes. There was no lesion which could have been identified or designated as the primary focus. These multiple subapical tubercles were combined with older and less old fibrocaseous tuberculosis with cavity formation and more recent massive intrabronchial spread.

#### GROUP I

*Case 1:* (B.G.H. 2645) Thirty-four year old white female. Cause of death: diffuse peritonitis following purulent appendicitis and salpingitis. (Plate 1)

The X-ray picture illustrates clearly the finding of six, in part nodular and partly rod-like lesions in the upper third of the left upper lobe within the subapical area. The regional bronchopulmonary and upper tracheobronchial lymph nodes show extensive cheesy-chalky changes. All these pulmonary foci were examined histologically. They showed considerable central chalky and calcific changes which were surrounded by broad hyaline-fibrous walls. In some of the foci firm, caseated matter, not completely calcified, was seen. There was no active tuberculous granulation tissue around the firm, caseated cores. Some foci were of oblong shape. The calcification was irregular, and some pictures suggested a direct connection of several of these lesions by firmly organized hyaline tissue. There was no bone formation present, although the centre of some le-

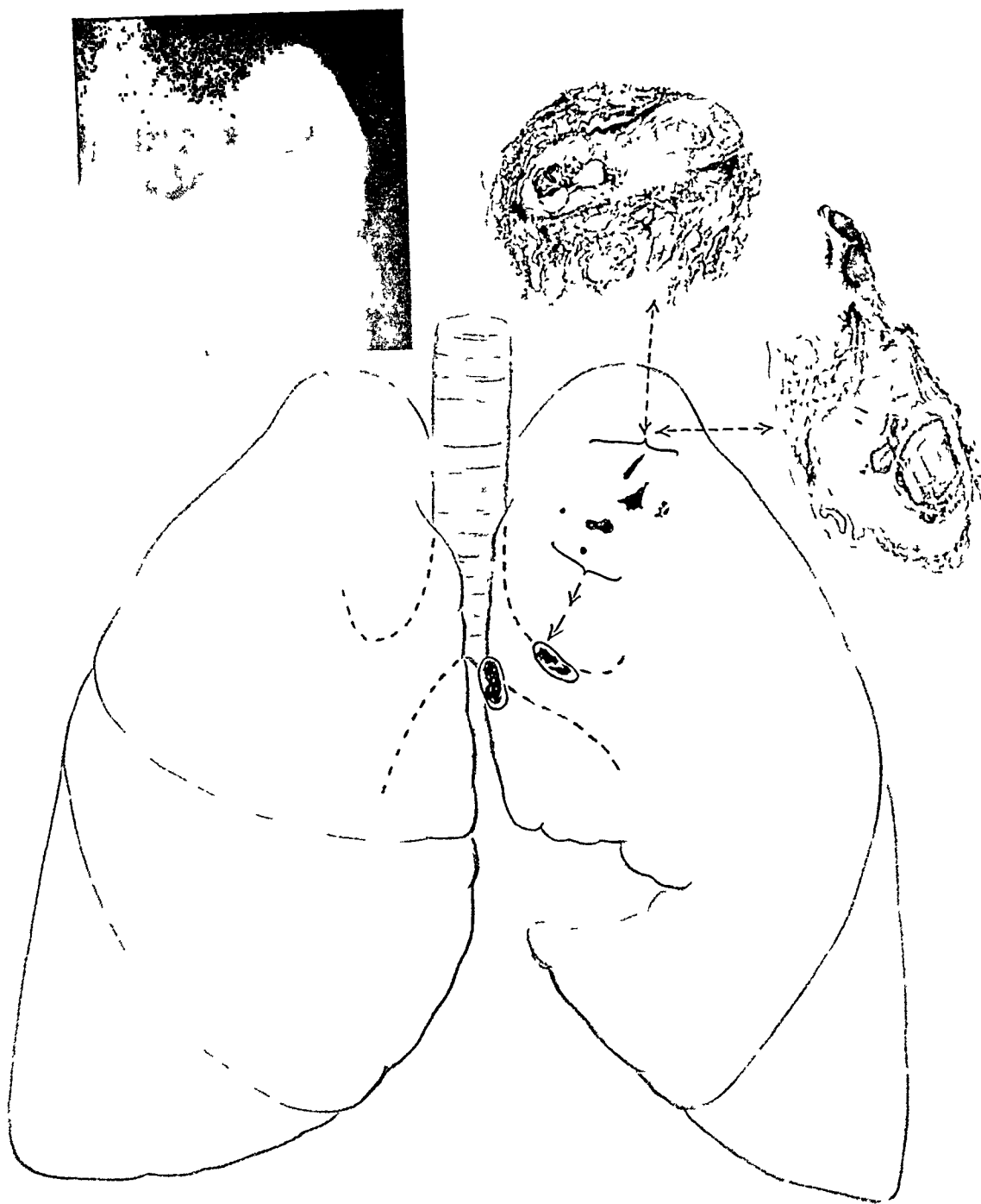


PLATE 1

sions appeared firmly calcified. Only in a few areas, surrounding chalky-fibrous tubercles, a few typical Langhans' giant cells were seen. In the apex of the right upper lobe a minute scar was found, histologically corresponding to collapse-induration, with emphysematous alveoli around. No specific change was present.

There was no evidence of any other tuberculous lesions in any organ.

There seems to be no doubt that in this case we are dealing with a chalky-calcified primary tuberculosis of the so-called "reinfection type," restricted to the subapical field. No single primary focus was discernible, but, rather, multiple older lesions, with the contiguity much closer than expected from the X-ray photograph alone. The original primary infection apparently had spread locally within the subapical area, merging with several focal lesions and infiltrations. That repeated superinfections of this restricted area in the early phase of the primary infection might have produced a similar scar cannot entirely be ruled out. There were no tuberculous lesions outside of those described; intestinal tract free, mesentery free, nowhere any hematogenous tubercles in particular. The extensive scar tissue around the hyaline capsules of the foci, along with localized anthracotic induration and a few emphysematous alveoli close to these scars, makes it most probable that the original tuberculous process was much more extensive, involving also those areas which now had resolved completely into nonspecific scars. The lymphogenous spread from the area of this first infection was restricted to two regional lymph node groups. The anatomical changes in these lymph nodes were in no way different from those seen in any typical primary complex.

The history does not contain any reference to a pulmonary disease. At no time was a tuberculin test done nor an X-ray photograph taken.

*Case 2:* (B.G.H. 3375) Fifty-nine year old white female. Cause of death: carcinoma of the gallbladder. (Plate 2)

In the right upper lobe, about 4 cm. below the apex, three calcified nodules were found within an area of about 1.5 cm. radius, varying between 3 and 5 mm. in diameter. Medial and rather close to these foci a distinctly larger, firmly caseated, bean-sized focus was found, showing on the cut surface a peculiar grayish-yellow, consolidated structure. This latter was diagnosed at gross inspection as an active tuberculous lesion. The regional bronchopulmonary lymph nodes about the bronchus draining the right upper lobe contained a few small calcified splinters, while the adjoining upper tracheobronchial lymph nodes partly in front of the major bronchus showed extensive calcification. There were no recent lesions of tuberculosis in any lymph nodes draining both lungs. The left lung was entirely negative except for a pinhead-sized, firmly calcified structure near the base of the left lower lobe. This, however, proved on histological examination to be a typical phlebolith. The pulmonary tissue between and around the calcified foci showed distinct localized atelectasis, especially in the subpleural areas in the periphery of the foci. The chart with the photographs shows the site and the histological type of all tuberculous lesions.

Our first impression, previous to histological analysis, was that we were dealing with an old, single primary focus without lymph node changes in the left lung and with a reinfection complex of older standing in the right lung, possibly with localized reactivation, as presented by the soft, grayish caseated focus found medially to the calcified lesions in



PLATE 2



the right upper lobe. Histologically, the entire area containing the calcified structures and the soft, caseated focus was examined, also the bronchopulmonary and right upper tracheo-bronchial lymph nodes, the calcified focus in the base of the left lower lobe and all bronchopulmonary lymph nodes draining the left lower lobe, in search for possible fibrous scars from older tuberculosis.

*Histological report:* All firmly calcified foci showed the typical picture of old tuberculous lesions encased by fairly complete and rather thick bony shells, attached to which firm stony matter was seen. Part of this was in process of resorption by bone marrow which contained fat cells, a large number of macrophages laden with anthracotic pigment, large lymphoid cells, few capillaries and a few small plasma cells. The close proximity of a fair sized artery proved that this huge bony focus apparently had originally included a smaller calibre bronchus. The surrounding area showed firm collapse-induration. The other foci were exactly of the same structure and almost the same size. In one of them the bony shell was slightly interrupted in a few areas, where somewhat anthracotic and relatively loose connective tissue seemed to grow actively into the stony core of the focus. There was much less bone marrow formation within this focus. Part of the bony shell was already split up into short fragments parallel to the original capsule, so that between these two bony fragments pigment-containing marrow was seen, eventually blending with firm, hyalinized connective tissue surrounding the focus. There was a small amount of anthracotic pigment in the firm stony core of the lesion. The smaller focus in the medial part of the upper lobe showed the same structure. The surrounding bony shell was relatively thick and fairly complete, only in one area interrupted by lymphoid marrow containing macrophages with anthracotic pigment. This was growing apparently actively towards the stony centre. The surrounding area showed considerable collapse-induration and, in addition, one pole of this focus was firmly attached to one markedly hyalinized anthracotic scar with alveolar emphysema of the adjoining pulmonary parenchyma.

The lymph nodes containing the firmly calcified matter showed, on histological examination, well outlined stony fragments, some of them very large, replacing almost the entire lymphoid structure, others smaller, found mostly in the capsule of the node. Only little hyalinized tissue remained between the stony fragments and relatively little anthracotic pigment. This picture corresponds to firmly encased stones, as seen in rather old lesions of tuberculosis. The findings in all lymph nodes are those of firm, stony tuberculosis, in some areas with unusually thick, completely hyalinized capsules surrounding the central stones, and with a few smaller tubercles in firmly hyalinized state within these capsules.

The grossly described large bean-sized, firm, caseated focus which was found near the mediastinal surface of the upper lobe at the level of the calcified lesions showed huge, caseated and slightly fibrous tubercles, in typical peribronchial arrangement, all surrounded by rather active tuberculous granulation tissue with many Langhans' giant cells and without any distinct encapsulation. Many smaller epithelioid giant cell tubercles were seen spreading gradually towards the surrounding lung tissue, which was slightly anthracotic. Some of the larger tubercles, of a more oblong shape, apparently followed the course of smaller bronchi. Several sections taken through the area of the recent focus prove that this tuberculous process was locally spreading farther than was anticipated at gross inspection.

There is hardly any doubt that we are dealing here with a relatively recent, true exogenous reinfection; in spite of its close proximity to the older lesions, there is a very distinct difference between those well encased, old primary foci and the fibrocaseated tuberculous reinfection. No spread from the recent tuberculous lesions to the lymph nodes draining this area was found in the few sections examined (no serial sections were taken).

If we disregard this additional finding of a true exogenous reinfection, this case is a clear demonstration of a primary lesion with three large foci and considerable anthracotic scarring between these foci in the right subapical area. In this final state it is impossible to judge the original extent of the lesion. It very well might have appeared at first as a much more marked and extensive, caseated infiltration than in this final obsolete state. Except for the additional lesions of clear reinfection character—a type which will be discussed in the forthcoming paper on localized exogenous reinfections—this case is almost identical with the former as to site and extent of the first lesion, although in a completely obsolete state.

Again, there was no history of a pulmonary disease at any time during the patient's life, and no record of a tuberculin test.

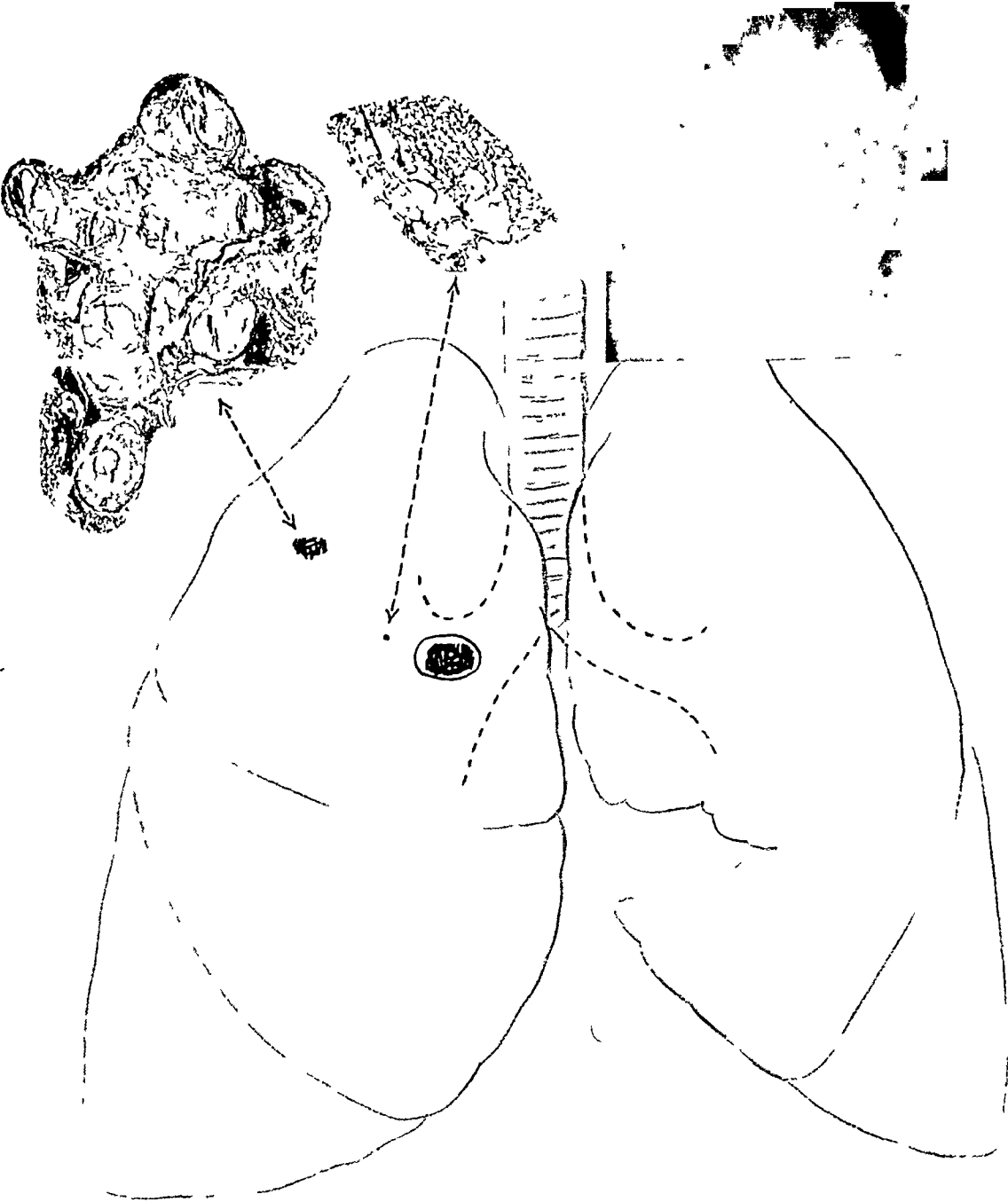
*Case 3:* (B.G.H. 2178) Thirty-four year old colored male. Cause of death: carbon monoxide poisoning. (Plate 3)

A small cherry-sized, firmly calcified focus is found in the middle third of the right upper lobe, with marked calcification of the regional bronchopulmonary lymph nodes. One single smaller calcified tubercle is seen in front of the right major bronchus. The histological picture shows a very close conglomeration of several firmly calcified foci encased by hyaline bands. In some of them, marginal bone formation can be made out, others show the typical picture of old, calcified, stony lesions. The intervening structures show very firm fibrosis with slight anthracosis. In some of the smaller calcified structures, surrounded by less dense connective tissue, a few foreign body giant cells can be made out. The histological analysis shows a picture usually not found in typical regressions of primary foci. It resembles much more changes seen in localized reinfections. In this case the tuberculous process apparently involved several smaller order bronchi and their peribronchial structures, but still near or at the margin of some focus occasionally a well preserved ectatic bronchus can be made out. In the van Gieson's stain, part of the remaining pneumonic structure in the centre of the stony lesions could be still recognized. Only a low view field actually shows the number of the small and larger stony fragments, here and there separated by air-containing and even emphysematous tissue. It seems as if the calcification in a few of the peripheral nodules is not as firm as in the others.

This case, then, represents apparently a primary lesion in the middle field of the right upper lobe. Though restricted to a relatively small area, on the X-ray film as well as especially on microscopic analysis, it appears to consist of several bronchial and peribronchial lesions which are not completely contiguous, and therefore resemble more the picture usually seen in old, locally spreading reinfections than in massive caseation of a single compact focus.

*Case 4:* (B.G.H. 4074) Forty-two year old white female. Cause of death: lymphatic leukemia.

There are several firmly calcified focal lesions varying in size from a lentil to small pea in the subapical field of the left upper lobe. They are mostly in the medial half, from 2 to 3 cm. below the apical area. A few, however, are more laterally, 1 to 2 cm. from the lateral surface. The X-ray photograph shows irregular dense shadows, varying from 2 to 5 mm. in diameter. The areas corresponding to the hilar region of the left upper lobe and along the major bronchus and trachea are entirely free of calcification. Histologically, the pulmonary lesions consist of very firm stones with almost complete bony rings. Some of the smaller foci are surrounded by very dense scar tissue with in-



complete ossification along the border. All are somewhat separated by atelectatic, indurated and partly anthracotic tissue, here and there, especially in the immediate neighborhood of the focal lesions, alternating with some emphysematous bullae. The apical portion shows collapse-induration with hyalinization and with a few huge bronchiectatic cavities without specific lesions in their walls, surrounded by emphysematous blebs. The lymph nodes regional to the left upper lobe did not show any evidence of tuberculosis on careful gross examination; no chalky or calcified changes, especially not on the X-ray photograph. They were not examined histologically.

Outside of this grossly and histologically typical obsolete tuberculosis of the subapical area, a reinfection complex was present with the parenchymal focus about 2 mm. in diameter in the left lower lobe, partly in hyalinized state, but—in the microscopic picture—with a well recognizable alveolar pattern. Two lymph nodes at the hilum of the left lower lobe showed soft, caseated, conglomerate tubercles which were surrounded by hyalinized capsules. These lesions could not be seen on the X-ray film; there was no trace of chalky material or calcification. They all could be easily cut with the knife at gross dissection. In addition, there was an obviously even more recent caseated focus in the right middle lobe, 2 to 3 mm. in diameter. This appeared, in the histological picture, only slightly encapsulated and surrounded by several epithelioid cell tubercles with focally spreading tuberculous bronchitis. There was no gross evidence of caseation in the lymph nodes draining this focus; they were not examined histologically.

We are apparently dealing with two, if not three episodes. The oldest tuberculous infection is presented by several stony lesions, in localization and structure similar to the obsolete subapical "reinfection type," apparently caused by the locally spreading original primary tuberculous infection of the left subapical field, without evidence of progression to the lymph nodes. Only a true reinfection brought about a localized and distinctly restricted complex formation apart from the old tuberculosis in the subapical field. There was evidence of hematogenous spread, possibly from the fairly recent focus in the right middle lobe, proved by a few rare, recent epithelioid cell tubercles with central necrosis in the liver. It is the old primary tuberculosis which had led to scars, grossly, in the X-ray film, in distribution and microscopic structure indicative of the so-called "reinfection type," while the true reinfection had produced a Ranke complex and was apparently followed by a localized superinfection with restricted perifocal spread and selective hematogenous tuberculosis of the liver.

In comparing the anatomical findings in these 4 cases just described, we have found that in 3 of them the type and extent of the lymph node changes regional to the area of the primary tuberculous infection are in no way different from any case in which this infection is presented by a single focus. Only in the last case there was no gross or X-ray evidence of calcified lymph node changes. Whether or not some microscopic fibrous tubercles have been missed in the regional lymph nodes remains undetermined, as, unfortunately, they were not examined histologically. Of particular interest is the third case, in which the X-ray picture suggested a single lesion of considerable size, whereas the complete histological analysis of the entire area showed that we are actually dealing with a focally spreading, though restricted tuberculosis, involving several smaller bronchi within this area, but still omitting part of the pulmonary parenchyma

between these lesions. Principally, this spread is not different from the more extensive subapical lesions in the 3 other cases, it is only considerably restricted. This case, without histological control, would have been classified merely as a typical large primary focus.

## GROUP II

*Case 1:* (B.G.H. 2056) Forty-four year old white male. Cause of death: tuberculous meningitis.

Only the condensed gross and histological report will be presented.

All tuberculous lesions were completely studied. In this case there were several ossified and calcified tubercles, from pinhead- to lentil-size, in the left apical and subapical field, a few of them rod-like. There was irregular scarring in the lung tissue in direct connection with the hyaline-fibrous capsules contiguous to the ossified lesions. Only in one left upper tracheobronchial lymph node a few minute, calcified splinters were found. In the right upper lobe, in the subapical area, there were a few, mostly smaller, firmly calcified tubercles of average pinhead-size. The lymph nodes regional to the right lung were free of tuberculosis. Histologically, four of the tubercles in the left upper lobe showed considerable bone formation, with bone marrow resorbing the remnants of the stony tubercle. The others were firmly calcified, encased in hyaline walls. The calcified tubercles in the right subapical field were in a firm stony state.

In addition, there were a few fibrocaseous, conglomerate tubercles, some of which had replaced smaller bronchioli, occluding their lumen. These were scattered over both lungs in relatively small numbers, and a few of them were found also in the lower parts of both subapical fields. Finally, there was a more recent, infarct-like *tuberculous* infiltration in the right middle lobe, involving several smaller bronchi within this area, surrounded by a distinct hemorrhagic zone. Around both upper lobes there were firm, fibrous adhesions, especially at the anterior aspect of the left upper lobe.

The remaining findings of tuberculous nature included firm caseation in the isthmic portions of both tubes and caseated tuberculous endometritis, rather numerous miliary tubercles in the liver and in the spleen, tuberculous infiltrations in the kidneys, a few small tubercles in the myocardium and diffuse tuberculous meningitis without tubercles in the brain substance.

There is no possibility to differentiate in this case between the primary complex and the old postprimary subapical lesions. Whether the primary pulmonary lesion somewhere in the upper portion of the left upper lobe had directly extended by localized intrabronchial spread within this area or was followed by superinfections of this subapical field cannot be determined at this late obsolete state of all these ossified and firmly calcified tubercles. The lesions in the right subapical area are of postprimary nature. There was no lymphogenous progression on this side.

No single lesion was found which could have been designated as the primary focus, although one upper tracheobronchial lymph node draining the left upper lobe contained a few small calcified splinters, pointing to the left apical or subapical field as the area of the primary infection. The small fibrocaseous tubercles which were found in relatively small numbers scattered over all lobes were most probably caused by hematogenous spread in connection with the chronic caseated tuberculosis of the genital tract. There was no evidence of recent

intrabronchial progression, except for a localized area of infarct-like appearance in the right middle lobe. Whether the recent hematogenous dissemination terminating in tuberculous meningitis had its direct source in the genital tuberculosis or in the more recent, in part hemorrhagic, tuberculous infiltration in the right middle lobe, with typical acute tuberculous bronchitis and peribronchitis, is impossible to state. There were no recent tuberculous lesions in any lymph nodes draining both lungs, which were completely examined microscopically. It is only fairly certain that the old primary or postprimary tuberculous infiltration of the left upper lobe was the source for the hematogenous tuberculosis, involving especially the genital organs.

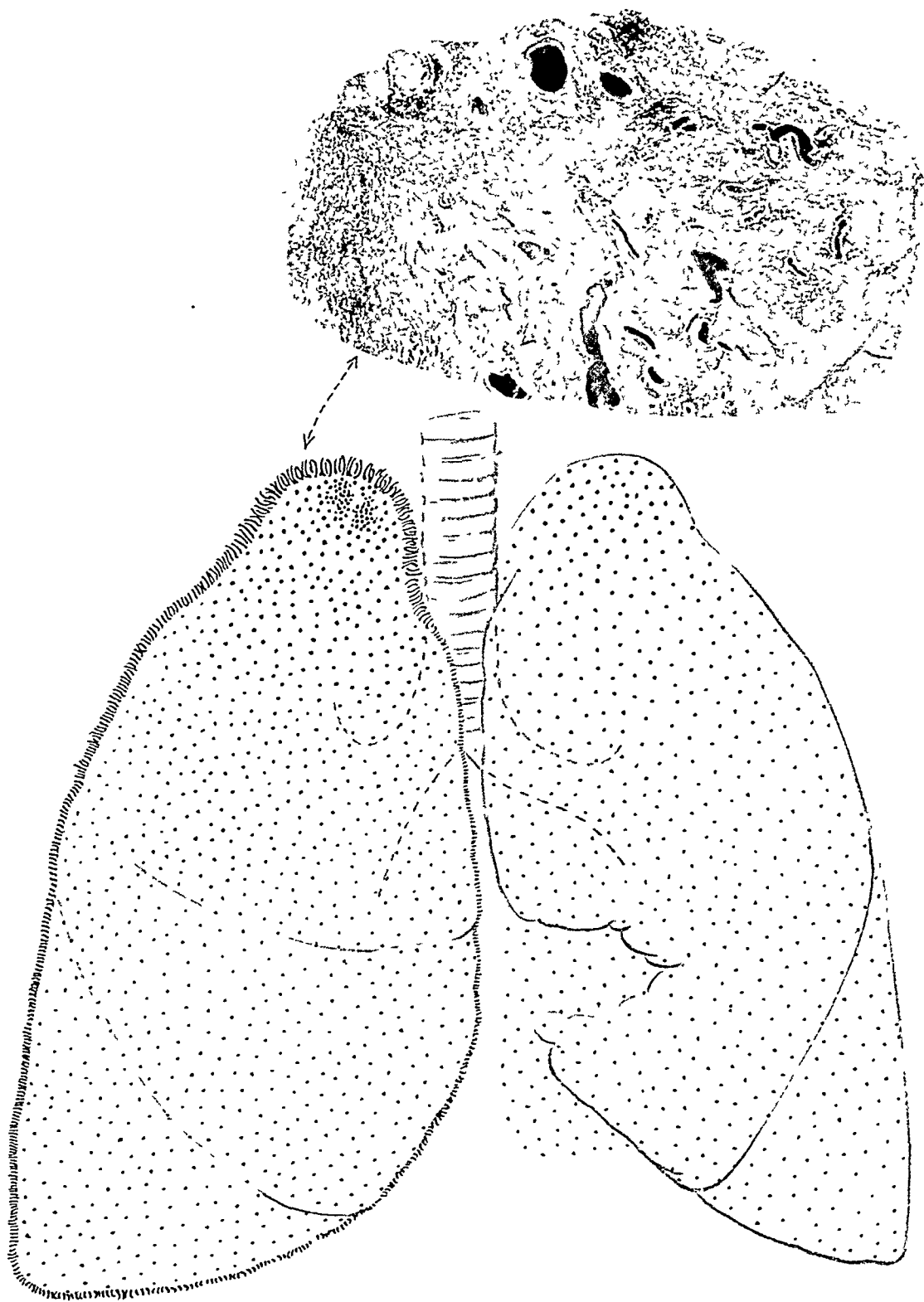
Unfortunately, the history of this interesting case is very fragmentary. The patient, a white, unmarried woman, forty-four years of age, was admitted seventeen days previous to death with oncoming symptoms of tuberculous meningitis. She was in poorly nourished condition. There was slight dyspnea but no cough; coarse breath sounds and a few crepitant râles in both apices. No X-ray picture was taken, as the patient's failing health was dominated by the rapidly unfolding state of tuberculous meningitis (with acid-fast bacilli in the spinal fluid). It is known, however, that the patient was treated for tuberculosis sixteen years previously, where and by whom could not be ascertained. No record of this disease, which might have been the result of her first infection, was obtainable. Whether or not an X-ray photograph was taken at that time is not known. It is the anatomical picture, only, as seen at the time of death, which suggested that the primary infection in this case might have merged into a typical subapical spread, either directly or by additional superinfections, which, we believe, justifies the inclusion of this case in this series.

*Case 2:* (B.G.H. 5308) Forty-two year old colored female. Cause of death: miliary tuberculosis. (Only the findings pertaining to tuberculosis will be listed.) (Plates 4a and 4b)

*Macroscopic report:* There were several firm tubercles of average lentil-size in the subapical field of the right upper lobe in very close relation to the pleura, imbedded in indurated, anthracotic tissue with unusually dense adhesions between the upper lobe and the parietal pleura, spreading from here around the entire right lung which was entirely fixed to the wall of the thorax, the diaphragm and the pericardial sac. No other firm tubercles were found anywhere in the lungs. The subapical portion of the right upper lobe, especially between the tubercles mentioned and the apex, appeared considerably indurated and in part anthracotic, while already at gross inspection next to these indurated areas a few small emphysematous blebs could be seen, especially on the surface of the lung. A few pea-sized tubercles in the same area were in a firm caseated state and appeared in close relation to the hyalinized and slightly anthracotic tubercles.

All lymph nodes regional to the right upper lobe were very carefully dissected. There was rather firm anthracotic induration in one of the upper tracheobronchial group but, except for a few recent miliary tubercles, no older tuberculosis could be detected grossly.

The X-ray picture shows complete absence of any lesion pointing to chalky or calcified changes. Both lungs showed, in very uniform distribution, dense miliary tuberculosis with soft tubercles varying in size from hardly discernible miliary to almost pinhead-



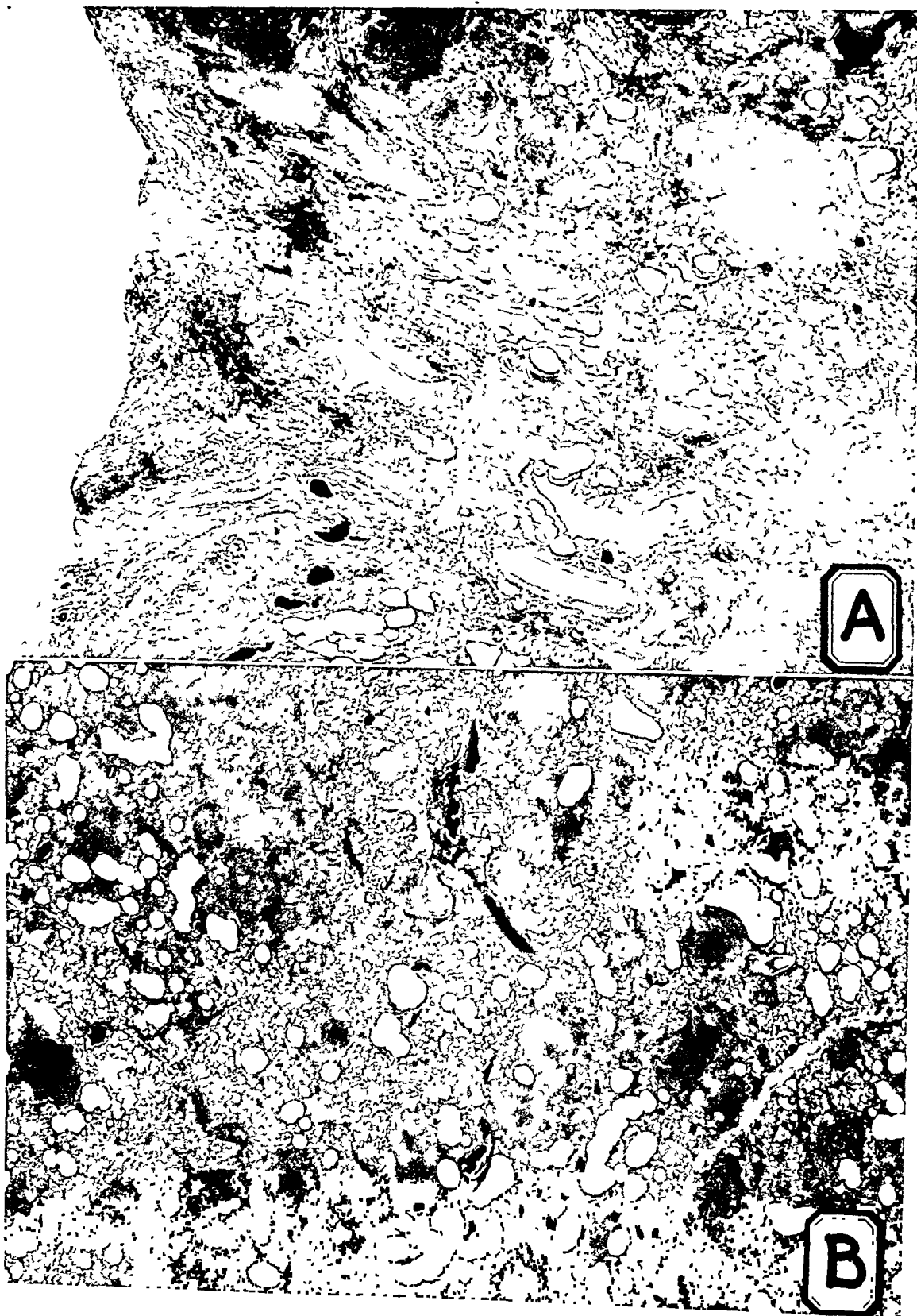


PLATE 4b



sized nodules. These tubercles appeared more prominent in the lower lobes, the right middle lobe and in the left upper lobe than in the remainder of the right upper lobe. All lobes were cut in fixed state in very thin sheets. There was no induration noticeable throughout all lobes except for the subapical area of the right upper lobe described above. All lymph nodes draining both lungs showed a few minute recent tubercles.

The source for this overwhelming miliary tuberculosis was apparently a very acute tuberculous caries of the first and second lumbar vertebral bodies with a small hazelnut-sized cavity very close to the intervertebral disc. There was, in addition, dense miliary tuberculosis in the spleen, liver and in each kidney, and a few small tubercles in the periportal lymph nodes. In connection with the caseated tuberculosis of the two lumbar vertebral bodies which had involved especially the posterior parts and extended very close to the spinal canal, two tuberculous psoas abscesses extended for a length of about 6 cm. along the lumbar spine, measuring from 1 to 1.5 cm. in width. There was very marked generalized marasmus.

The X-ray picture taken of the undissected specimen shows clearly the very dense miliary tuberculosis along with irregular small alveolar emphysema. A comparison between the left apical and subapical area and that of the right upper lobe shows irregular fibrosis or localized atelectasis in the latter. The complete absence of even the minutest spots pointing to calcification was rather an unusual experience in relation to the age of this patient.

The intestinal tract, along with the mesenteric and mesocolic lymph nodes, was entirely free of old or recent tuberculosis.

Some of the important histological findings in the right subapical area and especially a comparison between this and the left subapical area are indicated in table 1 and the photographs in plates 4a and 4b. The pictures show several old caseated tubercles surrounded by very distinct hyalinized walls, some of which show central disintegration. Others, somewhat smaller in size, are almost entirely hyalinized. Between these tubercles there is irregular hyalinization and distinct collapse-induration, especially in the subpleural areas. A few fair sized emphysematous blebs are included within this atelectatic, in part hyalinized area. A few small order branches of the pulmonary artery appear obliterated. Especially impressive is the area near the pleural surface, with a few oblong, completely hyalinized tubercles, some anthracotic induration, collapsed alveoli and a few irregular emphysematous blebs. Nearby there are huge, more recent conglomerate tubercles clearly formed in the wall of a bronchus, surrounded partly by already hyalinized, fibrous tissue, in other parts by tuberculous granulation tissue, while the remainder shows diffuse caseation. In other sections from this same area there are a few more recent conglomerate tubercles with central disintegration. Only within the areas showing complete collapse-induration there are no recent tubercles seen, but only distinct old, firmly hyalinized or caseated nodules. These correspond to the lentil-sized, firm tubercles grossly described which were fixed to the pleura. Some of the bronchi in sections taken from this entire area show slight ectasia with some accumulation of mucoid secretion. Especially these bronchi which are surrounded by emphysematous blebs walled off by entirely hyalinized tissue represent the so-called collapse-induration. A comparison between this area (A) and a slide taken from the left apical and subapical areas (B) proved clearly that there are only recent miliary and conglomerate tubercles in the left lung, and even these are of smaller size than the more recent tubercles in the right upper lobe. (See A and B on plate 4b.)

All sections examined from both lungs, apart from the right apical and subapical areas, show a uniform picture of acute miliary tuberculosis frequently leading to confluence of

these entirely caseated tubercles and to unusually marked inflammatory edema of the alveoli between tubercles. Also the emphysematous distention of some alveoli in different parts of the left lung is not as marked, in general, as in the right upper lobe. The acute miliary tuberculosis of the lungs seemed to have preceded the caseated bronchiolitis in several areas.

The histological picture of all lymph nodes draining left and right lung shows a moderate number of recent epithelioid cell tubercles. A few lymph nodes from the upper tracheo-bronchial group on the right side show quite marked anthracosis and extensive hyalinization of the reticulum, but in all sections examined just a few very small hyalinized tubercles could be seen in addition to typical recent epithelioid cell tubercles.

The histological picture of the lumbar vertebral bodies shows unusually marked liquefaction necrosis combined with firmer caseation, with a few small cavities containing obviously fluid debris and typical bony sequestrs. The entire border area of this tuberculous abscess shows the typical histological features of tuberculous osteitis and osteomyelitis.

*Epicrisis:* This case represents an older primary tuberculous infection of the right subapical and apical areas which had led to but few very typical, relatively small nodular hyaline-fibrous and fibrocaseated tubercles combined with typical collapse-induration and fibrous scarring, especially of the immediate subpleural area. There is but minimal and only microscopic spread to the regional lymph nodes, presented by rare, irregular, minute hyalinized tubercles. The tuberculous complex in the usual sense of the word is entirely absent. All the older foci are restricted to the right apical and subapical field; especially the dense and complete adhesions point to a preceding tuberculous pleuritis which apparently had started above the right upper lobe. The extensive caseated tuberculosis of the first and second lumbar vertebral bodies is secondary to the right subapical tuberculosis and is hematogenous in nature. The overwhelming miliary tuberculosis was apparently caused by the acute progressive tuberculous caries of the spine.

The history of this patient shows that the signs of tuberculous infection pointed first to the spine. She was admitted on February 18, 1943. Seven months previous to admission, in the summer of the preceding year, she had "pneumonia." Six weeks after apparent recovery she noticed severe pain in the lower back which recurred intermittently. This pain increased and extended downward to both thighs, especially on coughing and motion. There was some hyperesthesia in the right flank. The chest was clear. The spine showed very marked scoliosis to the right and slight lordosis. No pathological changes could be seen in the X-ray photograph of the spine in the middle of January. At the end of February the chest film showed soft, discrete infiltrations, diagnosed as miliary tuberculosis. Tuberculin test at this time was negative; no tuberculin test was taken at any time before. From the history of this patient it can be assumed that the condition diagnosed as pneumonia might have been a primary tuberculous infection of the right apical area with pleural effusion, as no remnants of primary tuberculosis were found elsewhere.

*Case 3:* (B.G.H. 3981) Eighteen year old white male. Cause of death: tuberculous meningitis. (Plates 5a and 5b)

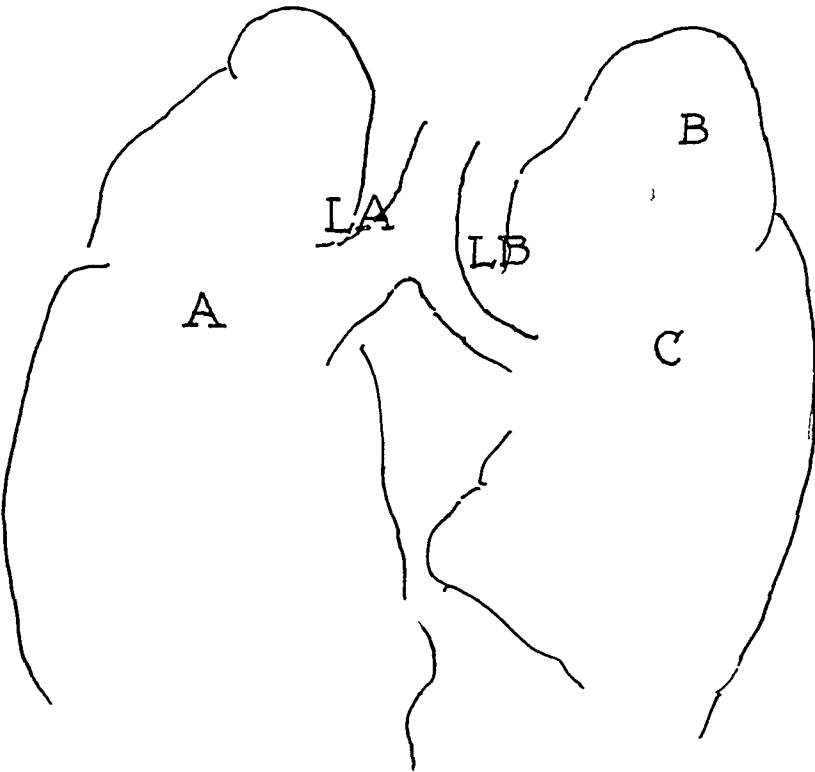


PLATE 5a



PLATE 5b

*Macroscopic report:* A primary complex is present with a well encapsulated focus 3 to 4 mm. in diameter in distinctly caseated state, with a soft, chalky centre, in the lower third of the right upper lobe near the hilum. There is considerable caseation with slight chalky changes in the regional bronchopulmonary and upper tracheobronchial lymph nodes.

Rather marked, in part firmly caseated bronchial and peribronchial tuberculosis of almost the entire subapical portion of the left upper lobe is found, especially in the central and lateral field, and in the apical portion of the left lower lobe. Several small caseated peribronchial tubercles are noted in the right subapical area and in the upper portion of the right lower lobe. All of the areas mentioned show grossly the typical picture of caseated lobular pneumonia in peribronchial arrangement. In the left subapical field and in the adjoining portions of the left upper lobe, involving mostly its apex, these tuberculous lesions are of a very compact, caseated bronchopneumonic appearance. The lymph nodes regional to the left upper lobe and the lower tracheobronchial lymph nodes on both sides grossly do not show any tuberculous lesions. There is, in addition, typical tuberculous meningitis with acute inflammatory hydrocephalus and recent aspiration pneumonia in both lower lobes. (A tuberculoma of the left cerebellar hemisphere had been removed surgically several days previous to death.)

The X-ray photograph of the undissected specimen very clearly reveals caseated and chalky changes in the right bronchopulmonary and upper tracheobronchial lymph nodes, also a faint shadow, pointing to the chalky centre in the primary focus. In addition, the almost wedge-shaped caseated infiltration in the left subapical area is very prominent. The large calcified structure above the left major bronchus proved to be a calcified thrombus in the ductus Botalli. (See plate 5a.)

*Histological report:* (See plate 5b and drawing on plate 5a.) The primary focus (A) is well encapsulated by a relatively thin fibrous wall and shows a typical diffuse caseated pneumonic structure with a small central, slightly chalky nucleus with the pneumonic pattern completely preserved. The regional lymph nodes (LA) show fairly diffuse caseation with distinct chalky changes. Most of their lymphoid structure is replaced by the huge firm, caseated and chalky tubercles.

Sections taken through the caseated infiltrations of the left upper lobe (B) show very huge bronchial and peribronchial tubercles, some of them considerably exceeding in size the primary focus, although decidedly of less old appearance without any chalky changes, but in part, at least, with distinct encapsulation. There are many more recent caseated tubercles of the typical histological pattern surrounding, in typical acinous arrangement, the huge caseated bronchial tubercles. Some of them show early central disintegration, while others are in a firm caseated state. The tuberculous changes in the subapical area of the right upper lobe appear of more recent character, with huge conglomerate tubercles surrounded by many typical giant cells, also of distinct acinous arrangement. The bronchial and peribronchial tubercles in both lower lobes (C) show a similar histological picture.

In the upper tracheobronchial lymph nodes regional to the left lung, a few recent conglomerate tubercles with central caseation were found (LB). (These were not recognized grossly.)

*Epicrisis:* It is difficult to state definitely whether or not the tuberculous findings in both lungs are related to a single infection which first had established the primary focus in the hilar area of the right upper lobe, with fairly massive complex changes in the regional lymph nodes. The primary focus,

in particular, appeared still in a diffusely caseated state; the surrounding capsule was relatively thin.

The entire gross picture with the massive caseated tuberculosis, affecting in wedge-shaped manner a rather huge area involving the entire subapical field (corresponding largely to the infraclavicular area) of the left upper lobe—opposite to the site of the primary focus—is, in our opinion, suggestive of a superinfection with consecutive intrabronchial spread to the right subapical area, and in scattered fashion to the upper portions of both lower lobes. The apices were not involved. This superinfection was probably also responsible for the hematogenous tuberculoma of the cerebellum, the removal of which was rapidly followed by tuberculous meningitis. There was no other evidence of hematogenous seeding.

The gross and X-ray picture of the postmortem specimen again would suggest that clinically this case could have been diagnosed as primary tuberculosis in the left upper lobe of the “reinfection type.” The faint chalky change in the lymph nodes regional to the primary focus in the right lung would hardly have been visible, and the primary focus would naturally have been entirely missed, as it was most difficult to recognize even on the roentgen photograph taken postmortem.

The first symptoms pointing to the tuberculous infection were those of frequent dizziness in the weeks preceding his admission, which was on August 20, 1938. The dizziness was so marked that the patient fell down several times. In February, 1938 the vision became impaired and headache developed. An X-ray film at this time did not suggest any tumor-like lesion in the head. There was no history of tuberculosis in the family. On admission there were decreased breath sounds and decreased resonance in the left posterior chest, with fine râles. An X-ray film showed changes suggestive of “chronic” tuberculosis in the left upper field.

As stated in the introductory remarks, this case appears as a classical representative of massive exogenous superinfection in a relatively early and still anatomically active phase of an otherwise typical primary complex. The absence of comparable massive lymph node changes regional to the left upper lobe proved clearly the postprimary character of this massive infiltration. Just as in the 2 preceding cases, it is again a hematogenous metastasis which determined the further course of the tuberculous infection. This case has a striking similarity to one published by Kudlich and Reimann (32), in which a similar infiltration of fairly recent nature in the left upper lobe had been diagnosed clinically as an Assmann infiltration. In this case, too, the clinical picture suggested a brain tumor, and the surgically removed tumor was a tuberculoma of one frontal lobe. In the discussion of the clinical history and the postmortem findings, Kudlich and Reimann felt that the subapical infiltration which was found in a relatively recent caseated state was the result of a second exogenous infection. In their case the primary complex had reached a much farther advanced state of regression than in ours.

*Case 4:* (B.G.H. 4204) Thirty-six year old white female. Cause of death: tuberculous meningitis. (Only the findings pertaining to tuberculosis will be mentioned.) (Plates 6a and 6b)

Postmortem there was a primary, chalky-calcified complex present with the primary focus pea-sized, in the middle third of the left upper lobe, and localized tuberculosis of one nearby bronchopulmonary lymph node, containing two pinhead-sized, chalky-calcified nodules. There were, in addition, a few calcified tubercles in both subapical areas, restricted to the upper third of each lobe, with slight atelectasis especially near the apical portions, and minimal thickening of the visceral pleura above these areas. The location and size of these subapical tubercles is seen on the roentgen photograph. Neither the lymph nodes draining the right upper lobe nor the lymph nodes above the left major bronchus and in the left paratracheal chain showed any gross evidence of tuberculosis. (Plate 6a.)

There were the following findings of active tuberculosis: Caseated osteitis and osteomyelitis in the midportion of the first left rib, broadly extending into the manubrium of the sternum. The tuberculous process of the rib had involved the intercostal musculature between first and second rib, forming a cherry-sized, cold abscess and a dime-sized ulceration in the skin above this area. At the hilum of the spleen, fixed to the tail of the pancreas, there was a walnut-sized, cheesy abscess closely adherent to the wall of the splenic vein but not extending into its lumen. Several nearby lymph nodes, attached to the tail and above the body of the pancreas, were considerably enlarged and showed diffuse cheesy and slightly chalky tuberculosis. Similar changes were found in a few paraaortic lymph nodes which were only moderately enlarged. In the wall of the thoracic duct, about 2 cm. above the angle of the azygos vein, there was a firm, caseous chalky tubercle, considerably pressing upon the lumen of the duct. Its proximal portion showed firm caseation involving a hazelnut-sized lymph node attached to the posterior wall of the superior vena cava just below the entrance of the right jugular vein. The entire lower portion of the thoracic duct was moderately distended, measuring 2 to 3 mm. in diameter. There were many millet-seed sized miliary, and a few pea-sized, conglomerate tubercles in the liver, but only very few miliary tubercles in the spleen. There were no grossly visible tubercles in the kidneys and adrenal glands. A typical tuberculous basal meningitis was seen with many minute tubercles in both Sylvian fossae and marked accumulation of spinal fluid in the cisternae, also many tubercles in the choroid tela of the third ventricle. There were no tubercles in the central nervous system proper (the entire brain, cerebellum and brain stem were examined macroscopically in thin slices).

There were no grossly noticeable miliary tubercles in the lungs.

*Histological report:* All calcified and chalky-fibrous lesions found in both upper lobes and the lymph nodes draining both lungs were examined. (Plate 6b.) The parenchymatous lesion near the hilum of the left lung presenting the primary focus (A) contained a small calcified nucleus within a huge chalky area which was surrounded by a fibrous-hyaline wall, with a few bud-like hyalinized protrusions. This wall showed a distinctly irregular thickening. All lesions found in both subapical areas showed a very similar structure (B and C). They were only of slightly smaller size than the primary focus. All these lesions were in a firm, chalky-fibrous state, with more or less marked central calcification. In each subapical area there was, in addition, a firmly hyalinized intrapulmonary lymph nodule containing a well outlined calcified conglomerate tubercle. The lesions in the right subapical field did not show any difference in size nor anatomical structure from those in the left lung. The shape and location of a few of the larger tubercles in each subapical area seemed to correspond to smaller bronchi. Nowhere were

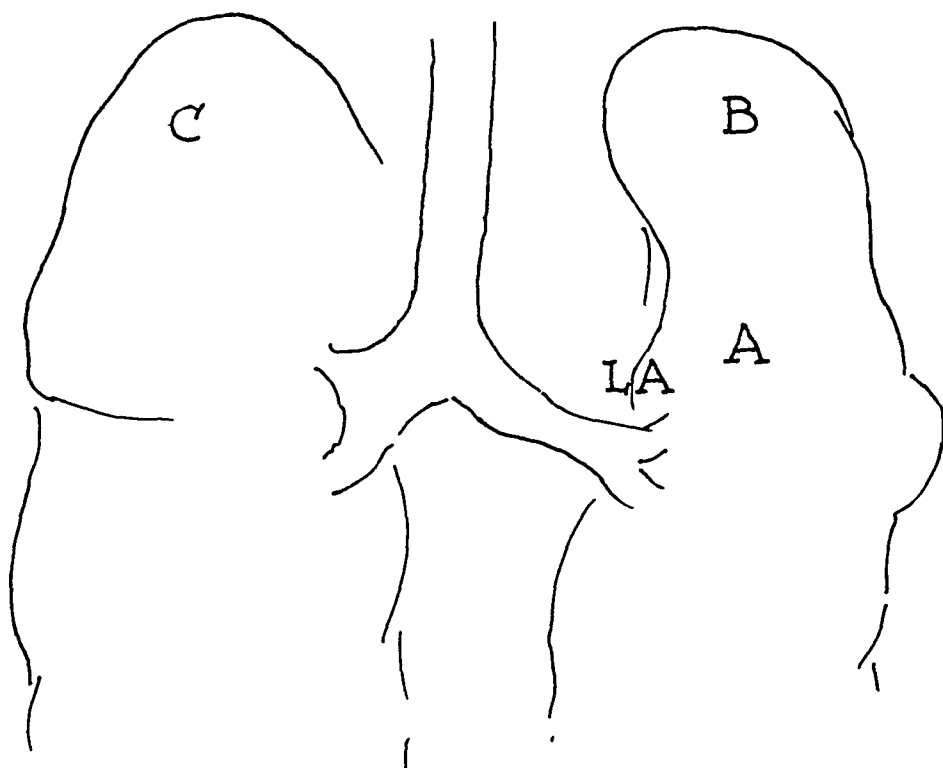
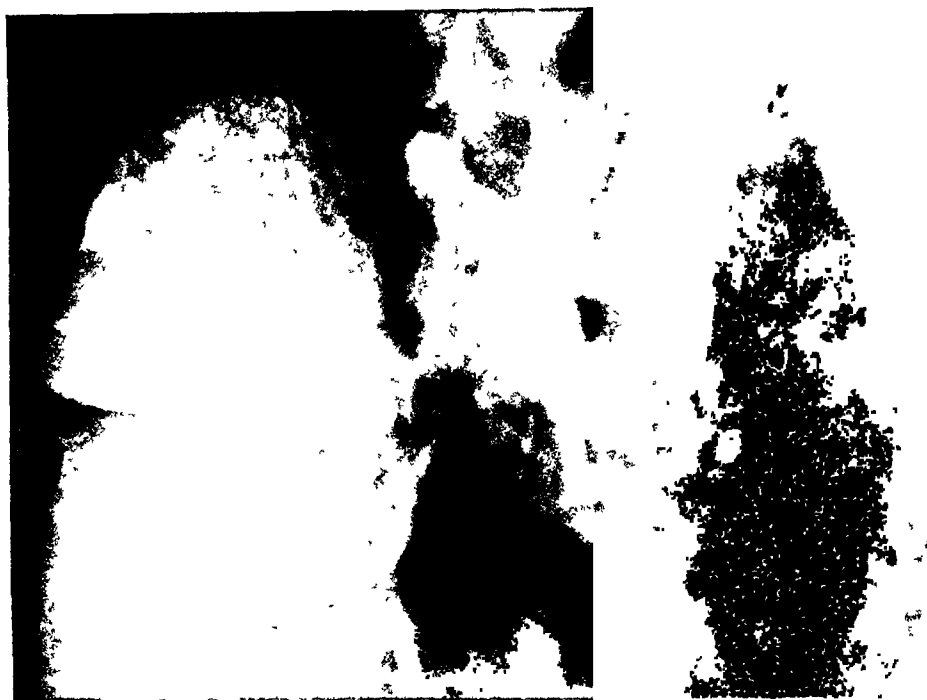
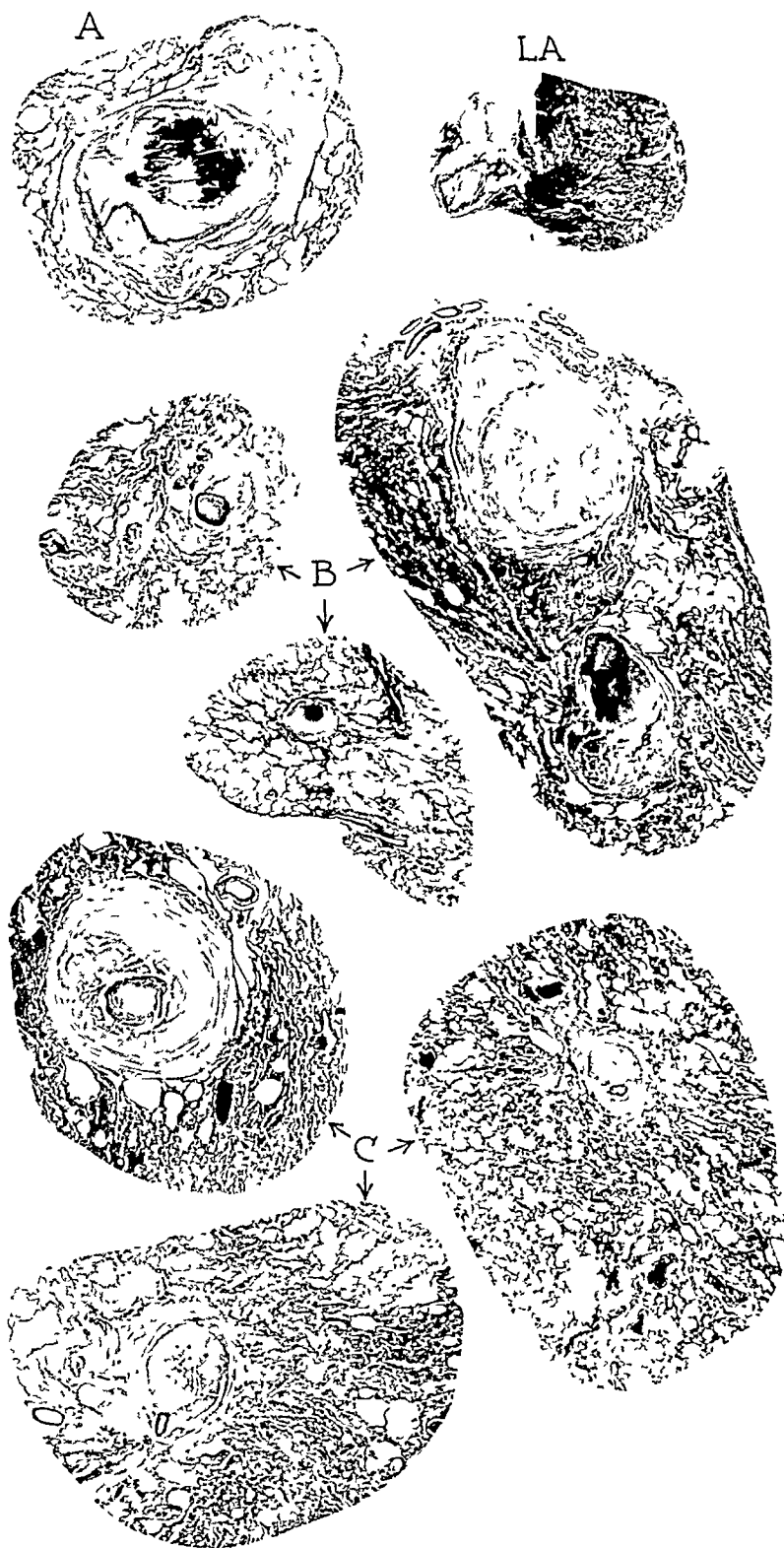


PLATE 6a





there any recent tuberculous lesions in the areas surrounding these chalky-fibrous and calcified tubercles. In comparing the roentgen photograph with the histological structure of the individual calcified and chalky-fibrous tubercles found in both upper lobes no difference in the intensity of calcification could be noticed on the X-ray film. In fact, the primary focus, as revealed on sectioning, seemed to include some soft, not entirely calcified, chalky material in its centre. The hyaline-fibrous encapsulation around the chalky and diffusely caseated core was not more marked in the primary focus than in most of the chalky-fibrous tubercles found in both subapical areas. It was mentioned already that the primary focus was slightly larger than the subapical tubercles. It contained a good amount of soft, caseated-chalky material, with cholesterol crystals near its centre. On the other hand, the small conglomerate tuberculous lesion found in one intrapulmonary lymph nodule in each subapical area included a rather firm, chalky-calcified structure, apparently very near to stone formation.

Gross, roentgenological and histological analysis strongly suggests that these subapical lesions in both upper lobes had developed in very close connection with the primary lesion. In this moderately advanced state of calcified, chalky-fibrous encapsulation, no arbitrary decision can be made whether the scattered subapical tubercles in both lungs are the result of a superinfection during the still active phase of the primary focus, or whether they were more directly related to this focus from which both subapical fields became gradually involved by intrabronchial spread. The focus in the middle third of the left upper lobe was believed to be the primary lesion because of its close topographic relation to one nearby chalky-calcified anterior bronchopulmonary lymph node at the hilum of this lobe (LA).

There were also a few recent scattered tubercles in all lobes of both lungs which were not recognized grossly but were found, incidentally, in the routine examination of different sections taken from both lungs. These recent lesions were caseated, small conglomerate tubercles; some of them were seen in the walls of smaller bronchi, surrounded by a few epithelioid cell tubercles. (This localized caseated tuberculosis in the wall and lumen of smaller bronchi has been frequently observed in cases of protracted hematogenous tuberculosis by Schuermann.)

All apical and subapical lesions in both upper lobes were of the same firm fibrous-chalky and chalky-calcified character, encased within rather thick hyaline-fibrous capsules, and had a decidedly older structure than the few small hematogenous tubercles scattered over both lungs. They appeared in a state of advanced healing. Except for localized atelectasis caused by old chalky-fibrous obliteration of a few small order bronchi, the area surrounding all these foci noticed on the roentgen film was well aerated.

This old subapical tuberculosis, which, we believe, might have originally coincided with, or soon followed the primary infection, had led to a slowly progressive hematogenous seeding involving the first left rib and the lymph node groups at the hilum of the spleen, around the pancreas and around the upper part of the abdominal aorta. Whether or not the tuberculous meningitis was caused by the massive caseation of the thoracic duct or by the still active tuberculous osteomyelitis of the sternum and the first rib, cannot be decided.

The contrast between the large number of tubercles in the liver and the very few scattered tubercles in the lungs, found only microscopically, was rather unusual. This massive tuberculosis of intraabdominal and retroperitoneal lymph node groups has also been observed occasionally in cases of protracted hematogenous tuberculosis. The tuberculosis of the thoracic duct had apparently developed contiguously to the extensive caseation of the lymph nodes at the hilum of the spleen and above the pancreas.

The history, as given in the chart of the patient, does not contain any data referring to the primary pulmonary infection which apparently had occurred a considerable time previous to death. The patient, a married housewife, was admitted on May 17, 1939. The first symptoms pointing to tuberculosis appeared twelve months previous to admission, at which time an ulceration developed about one inch below the middle of the left clavicle in the skin covering the first intercostal space. Only for the last three months there was draining of purulent exudate from this ulcer. At clinical examination the chest was found entirely clear. When the patient was admitted, her symptoms already pointed to an incipient tuberculous meningitis.

Roentgenological examination of the chest disclosed a few calcified nodules near the left hilar area. There is no record of a tuberculin reaction at any time. It is of interest to note that the patient had delivered a child in October, 1938. At this time, according to the chart, the tuberculosis of the first left rib had already produced an ulceration in the overlying skin.

*Case 5: (B.G.H. 3462)* Twenty-two year old white female. Cause of death: pulmonary tuberculosis.

Only a very brief report can be given of this case. There were several pinhead-sized, calcified tubercles in the subapical area of the left upper lobe. No single primary focus was found, but, in a few bronchopulmonary lymph nodes at the hilum of the left upper lobe and in the upper tracheobronchial group on the left side, a few minute stony tubercles were present. There was, in addition, a walnut-sized cavity in the lateral upper area of the left subapical field and massive recent tuberculosis of fibrocaseous character in all lobes, but especially in the right lung. The lymph nodes regional to the right lung did not show gross changes of tuberculosis.

Four years previous to admission the patient had complained of extreme fatigue. At this time the diagnosis of tuberculous infiltration of the left upper lobe was made. The patient was under sanatorium care for three years. She suffered from a massive pulmonary hemorrhage toward the end of the first year of her disease, and pneumothorax treatment had been given since that time. Death followed lysis of adhesions around the left upper lobe, with development of a bronchial fistula.

In this case the histological examination was not permitted. The gross and X-ray picture, however, seems to point to a chronic tuberculosis with progressive intrabronchial spread, in which the primary lesion either had merged into a gradually spreading subapical tuberculous infiltration, producing a cavity, or was followed by massive superinfection. There was distinct lymphogenous spread

from the area of the first infection. For lack of histological control of any lesion, this case will be excluded from our following discussion.

#### DISCUSSION

In all cases included in the two groups, there was clear macroscopic evidence of lymphogenous progression to one or two lymph nodes or lymph node groups regional to the area of the primary tuberculous lesions, with two exceptions. In one of them, case 2 of group II, these changes were of microscopic nature; in the other, case 4 of group I, no histological control was available to decide the presence or absence of a microscopic lymph node complex change. The location of these apparently primary lesions was in all 4 cases included in group I in the upper part of one upper lobe, especially within the subapical area. Also restricted to only one upper lobe were the primary lesions in case 2 of group II. In the remaining 3 cases of group II, both subapical fields were involved. The presence of distinct scarring in the lung parenchyma between the subapical tubercles, along with findings of local collapse-induration, suggested for most of our cases that the original tuberculous infiltration of these areas had been considerably more substantial than the final, more or less obsolete state of the subapical tubercles could indicate.

Only in 2 cases of the entire series, nos. 3 and 4 of group II, a single primary focus could be clearly recognized, located in the upper lobe slightly above the hilar level. In one of these (case 4) the histological analysis did not disclose clearly whether the additional subapical lesions had been brought about by intrabronchial extension from the primary focus or by superinfection. All the parenchymatous lesions, including the primary focus, appeared in a fairly advanced state of healing. Case 3, however, we believe, represents a recent superinfection of one entire subapical area, distinctly apart from the primary focus. This focus and the regional lymph node changes were still in a state of considerable caseation, with slight and entirely soft chalky changes. It is interesting that the roentgenological examination in this case had disclosed only the tuberculous infiltration of the left upper lobe (diagnosed as "chronic tuberculosis"). The anatomical substrate of this infiltration was presented by lesions of distinctly postprimary character brought about by superinfection, while the primary complex with typical location and size of the focus and considerable extent and intensity of the regional lymph node changes was not recognized clinically. These anatomical observations regarding case 3, which might be applicable also to case 4, are of importance from the clinical diagnostic point of view. They are apt to support the conservative attitude of Stiehm and of Israel and Long as to the great limitations for the clinical diagnosis of tuberculous lesions in the upper lobes of young adults in specific pathogenetic terms (as to the primary or so-called "reinfection type").

From the material presented in this paper, it can be said that primary tuberculous infection can occasionally involve a more or less broad area in one subapical field, more or less close to the apex. In a few observations this area corresponded to the so-called infraclavicular field. These tuberculous changes,

as judged from their topographic-anatomical and histological analysis, were apparently established by localized intrabronchial spread leading in the later involutionary stages to several calcified and ossified local lesions with intervening fibrous scarring. In addition, this study has revealed that lesions similar in character and location, restricted to one or both subapical areas, might develop in the presence of a typical primary complex not as yet healed. In these instances the clearly postprimary character of the subapical lesions points, in our opinion, to true (exogenous) superinfection as the most likely pathway. In no one of our observations was there any anatomical sign which could have suggested a blood-stream infection preceding the establishment of these subapical lesions. The anatomical picture in all of them clearly pointed to a close relation to smaller bronchi, regardless of whether or not these lesions had simultaneously developed or were caused by superinfection in the presence of a typical primary complex, still caseated.

Except for case 3 of group II, representing a progressive superinfection with hematogenous spread to the brain and intrabronchial extension within the lungs, the apical and subapical lesions had remained restricted to the area of the original primary or early postprimary infiltration. There was no evidence of intrabronchial extension to other parts of the lungs. These lesions were in an obsolete or advanced state of regression. On the other hand, in all 4 active cases included in group II, the fate of the patients was determined by hematogenous metastases from these subapical primary or early postprimary lesions. These hematogenous metastases, in the skeleton in 2 cases, in the genital organs and in the brain in the other 2, dominated the disease picture, leading to overwhelming miliary tuberculosis in one and to a more protracted form of hematogenous tuberculosis in the 3 other cases. All of these latter, however, terminated in tuberculous meningitis. The scattered recent pulmonary tubercles, which were found in all lobes in 2 of these cases, were few in number, small, and apparently of hematogenous nature. There was no direct pathogenetic link between these and the old primary or postprimary subapical lesions.

Of particular interest is case 4 of group I, in which a typical reinfection complex was found which apparently was followed by an even more recent focal superinfection, while the remnants of the old primary infection were represented by several completely obsolete tubercles in typical subapical location without gross or roentgenological evidence of a lymph node complex formation.

In the discussion of the incidence of these apical and subapical tubercles of apparently primary character, we have to omit cases 3 and 4 of our group II, in both of which a single primary focus was present in addition to recent (case 3) or older (case 4) postprimary lesions. There remain, then, 6 instances out of a total of 330 postmortem observations with various anatomical findings of tuberculosis. This represents about 1.8 per cent. The relationship of the 2 cases (nos. 1 and 2) of group II with fatal tuberculosis to all cases of active progressive tuberculosis in our material is about 2:55 or 3.6 per cent. We should not attach any great significance to this figure, as the number of patients dying from tuberculosis is naturally small in a general hospital, even over a period

of eleven years. How far they might differ from comparable observations on a large series of adult tuberculosis patients treated in sanatoria, only the future will tell.

In a previous paper on recent primary tuberculosis in adults (10), the anatomical findings in 16 cases were tabulated, in all of which a typical primary complex in cheesy, cheesy-fibrous or cheesy-chalky state was present, pointing to a late primary infection. Their ages ranged from twenty-eight to eighty years. Since that time, similar incidental observations were made on 12 additional cases. Six of these were from twenty-two to thirty-nine years old, the other half between fifty and sixty-four years. Neither the location of the primary foci in all of these, nor extent and degree of the regional lymph node changes differed from that known from primary complexes in children.

Our findings, then, presented in this paper, especially in their proportion to the entire material examined morphologically, do not support such general claims that primary tuberculous infection in the adult leads directly to a tuberculous process involving the apical and subapical areas of one or both lungs. Although one feels naturally reluctant to formulate laws regarding the pattern of a disease process, like tuberculosis (and others), about which we have learned of a multitude of individual variations, we believe there is no anatomical basis for the claim that primary tuberculous infection of the adult usually localizes in more or less diffuse fashion in the apex or subapical area. Our few observations reported above appear, in our limited experience, as uncommon occurrences rather than as the rule. We hope they will stimulate continued, careful anatomical search, to learn more of the relative frequency and importance of these lesions.

#### SUMMARY

This morphological study was undertaken to determine how far clinical observations, suggesting that primary tuberculosis in adult life produces directly a more or less diffuse infiltration of the apical or subapical areas, could be supported by anatomical evidence obtained from detailed gross and histological analysis. Of 330 cases with various anatomical findings of tuberculosis, including 55 cases of fatal tuberculosis, localized tuberculous lesions from 1 to 5 cm. below the apex, without a recognizable primary focus, were present in only 6 instances. In 4 of these, there was clear macroscopic evidence of corresponding lymph node changes in one or two lymph node groups regional to the subapical area containing these apparently primary lesions. There were 8 cases altogether, completely analyzed in this study. In 4 (group I), such apical and subapical findings were of incidental nature and in a more or less advanced state of scarring. Of the 4 cases of fatal tuberculosis included in group II, only in 2, similar subapical lesions were found which represented the result of a primary pulmonary infection. In the other 2, these subapical lesions were of postprimary character, pointing clearly to exogenous superinfection as the pathogenetic mechanism in one, with a typical primary focus still in a caseated state and massive tuberculous caseated infiltration of the opposite subapical

field. The clinical X-ray diagnosis in this case was "chronic apical tuberculosis"; the typical primary complex was not recognized roentgenologically. The same pathway seemed probable in the other of these 2 cases, in which primary focus and postprimary subapical tubercles were both in an advanced state of healing. In all 4 cases of group II, the subapical primary and postprimary lesions initiated a protracted hematogenous tuberculous process with metastases to different organ systems, including especially skeleton, genital organs and central nervous system, terminating in overwhelming miliary tuberculosis in one, and tuberculous meningitis in the 3 others. In our material so far studied, this apparently primary tuberculous infiltration of the upper portions of one upper lobe proved a rather infrequent occurrence, below 2 per cent of the total incidence of tuberculous lesions found postmortem in 330 adult cases. If only the cases of acute or chronic fatal tuberculosis are included, this percentage is below 4.

#### SUMARIO

Emprendióse este estudio morfológico a fin de determinar hasta qué punto encuentran apoyo en los datos anatómicos obtenidos en minuciosos análisis macroscópicos e histológicos las observaciones clínicas indicativas de que la tuberculosis primaria de la vida adulta produce directamente una infiltración más o menos difusa de las zonas apicales o subapicales. De 330 casos con varios hallazgos anatómicos de tuberculosis, comprendiendo 55 casos de tuberculosis letal, sólo en 6 había lesiones tuberculosas localizadas de 1 a 5 cm. más abajo del vértice, sin foco primario reconocido. En 4 de ellos había signos macroscópicos netos de correspondientes alteraciones de los ganglios linfáticos en uno o dos grupos pertenecientes a la zona subapical que contenía dichas lesiones aparentemente primarias. En este estudio analizanase completamente 8 casos en conjunto. En 4 (grupo I) dichos hallazgos apicales y subapicales eran de naturaleza fortuita y se hallaban en un estado más o menos avanzado de cicatrización. De los 4 casos letales comprendidos en el grupo II, sólo en dos encontráronse lesiones subapicales semejantes que representaran las secuelas de una infección pulmonar primaria. En los otros 2, esas lesiones subapicales eran de naturaleza postprimaria, señalando claramente la superinfección exógena como organismo patogenético en uno, con un típico foco primario todavía en estado caseado e infiltración caseada, tuberculosa masiva del campo subapical opuesto. En este caso el diagnóstico clínico roentgenológico fué "tuberculosis apical crónica"; el complejo primario típico no fué reconocido roentgenológicamente. La misma vía parecía probable en el otro de los dos casos, en el cual tanto el foco primario como los tubérculos subapicales primarios hallábanse en un período avanzado de cicatrización. En los 4 casos del grupo II las lesiones primarias y postprimarias subapicales iniciaron un proceso hematógeno prolongado con metástasis a diversos aparatos y sistemas del organismo, comprendiendo en particular el esqueleto, los órganos genitales y el sistema nervioso central, y terminando en uno en una granulía agobiadora y en meningitis tuberculosa en los otros tres. En el material estudiado hasta ahora esa infiltración tuberculosa aparentemente primaria de las porciones superiores de un lóbulo superior resultó algo

rara, representando menos de 2 por ciento de la incidencia total de lesiones tuberculosas descubiertas en la autopsia en 330 casos adultos, y si sólo se toman los casos de tuberculosis letal aguda o crónica, el porcentaje es inferior a 4.

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# ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS<sup>1</sup>

## XV. Restricted Pulmonary Reinfection

KORNEL TERPLAN

In a previous paper entitled *Nomenclature and Anatomical Methods* (1), the term "reinfection" was defined as a new infection with tubercle bacilli from without excluding any formal genetic relationship to the primary infection. It is this type of reinfection in the strictest sense which will be discussed in the present and following papers in referring to such cases only in which "all anatomical evidence points to a new infection from without in the presence of an actually healed or healing lesion." The term "superinfection" will be limited to such instances "in which an additional infection from without has taken place in an individual which still harbors an active tuberculous lesion." In dealing with later regressive changes of exogenous infections which, at least in part, are found already in a state of advanced healing, it is frequently impossible to distinguish between reinfection and superinfection. Both of these, however, are new infections from without (exogenous), and their anatomical effects appear entirely dissociated from the various results of the primary infection, including primary focus, lymph node changes and all metastatic lesions formed in connection with the original infection.

The problem, then, is to examine how far it is possible, morphologically, to relate the anatomical findings in pulmonary tuberculosis and tuberculous lesions in other organ systems to the primary infection alone, including all its direct or indirect sequelae, or to one or more new infections from without—the true reinfections and/or superinfections. The primary complex, or—in some instances—the primary focus alone, has the controlling position in the pathogenetic analysis of the various tuberculous lesions, incidentally found, as well as in the final stages of the various types of chronic pulmonary tuberculosis. We shall examine first—in the present paper—relatively restricted or even a few single focal lesions, the analysis of which, we feel, causes little difficulty. The following two papers will include cases of chronic pulmonary tuberculosis combined with more or less marked intracanalicular spread but with little or no evidence of hematogenous lesions (no. XVI), and a series of cases with considerable hematogenous involvement of both extrapulmonary organ systems and the lungs (no. XVII).

The anatomical material used for this paper includes incidental postmortem findings of more or less restricted reinfections in 28 cases, in none of which the cause of death was tuberculosis. Its presentation will be preceded by a brief résumé of the views expressed in the more recent literature on the nature of the "reinfections" and especially on their relation to primary tuberculosis.

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Of pathologico-anatomical investigations carried out on a large scale, the thorough studies of Schuermann (2) should be mentioned first. They were dealing with different types of acute and chronic tuberculous processes and their relation to hematogenous tuberculosis. Of 1,000 cases, in 27.1 per cent the chief postmortem finding was pulmonary tuberculosis. Only in one-fourth of these there was a combination with hematogenous tuberculosis, while three-fourths were cases of pulmonary tuberculosis without hematogenous metastases. Schuermann's material included also 5 incidental observations of more recent postprimary processes found in cases of accidental death. In almost all cases of progressive pulmonary tuberculosis in adults, remnants of a healed primary complex were found. According to Schuermann, apical and subapical tuberculosis, especially their beginning phases, are caused by exogenous superinfection.

Puhl (3), a pupil of Aschoff, also believes in the exogenous nature of chronic tuberculosis in adults. It is, according to Puhl, usually initiated by multiple reinfections in one upper lobe. Such reinfections were observed in 43 cases, 35 of which developed progressive pulmonary tuberculosis. We shall omit for the present any discussion of the question how far the anatomical-histological structure of these multiple or single "reinfects," which have been associated especially in the European tuberculosis literature with the name of Puhl, is specifically different from the primary focus.

Other proponents of the exogenous nature of the reinfections are Beitzke (4), Anders (5), Kalbfleisch (6) and Loeschke (7). Beitzke calls attention to the ever present sources for exogenous infections with tubercle bacilli, to which we are exposed throughout life. Anders has pointed out that the reinfection lesions in his anatomical material (with the exorbitant figure of 95 per cent) were usually seen in the absence of any gross propagation of the tuberculous infection from the primary focus. Loeschke found lesions of apical tuberculosis in the young adult usually with a "resting" primary complex, meaning the absence of any anatomical sign of activity in its components. I can put no trust in Blumenberg's (8) statement that remnants of a healed primary tuberculosis were usually absent in adult cases with fatal pulmonary tuberculosis which is entirely contrary to the results of Schuermann's exhaustive studies. A comparative analysis of the anatomical data in the papers of Schuermann and Blumenberg clearly reveals this. Blumenberg also claims that he has "very seldom" seen the reinfects of Puhl in fatal adult tuberculosis.

That Opie (9) is favoring exogenous infections in the pathogenesis of tuberculosis, as generally seen in adults, can be assumed when he states that anatomical evidence shows that the tuberculous lesions of adult life are not a continuation of the first infection. Referring to tuberculous processes as observed in young adults, Burrell (10), too, favors exogenous infection, or more specifically, superinfection added to a primary lesion in a "tuberculin reactor." According to Stefko (11), Abrikossov was one of the first to stress the independence of the reinfection from the primary tuberculosis. This view, however, was apparently not shared by Stefko, himself. Even Huebschmann (12), who has re-

peatedly stated his belief in the alleged hematogenous metastatic nature of apical tubercles, admitted that there is no proof that the entire picture of tuberculosis, as we see it in men, is caused by a single infection.

In the preceding paper the great limitations to correct clinical diagnosis in regard to primary infection, superinfection, or reinfection in adults, especially in the absence of sufficiently complete serial data on tuberculin reactions, were referred to. We shall include, therefore, in this discussion, only a few statements based on considerable experience in clinical observations. To Lange (13), medical practice reveals the great importance of exogenous superinfection. This superinfection appears very significant also to Kayser-Petersen (14), not only in its disastrous effects as he has seen them especially in children, but also in their entirely harmless results as incidentally discovered in healthy adults. Kayser-Petersen also quoted the views of Adler (formerly in Prague), that exogenous reinfection is not prevented by primary tuberculosis acquired in childhood. Malojcic (15), after five years of close study of 1,126 inhabitants of a small rural community, came to the conclusion that repeated exposure to open cases of pulmonary tuberculosis is a greater danger to already infected adults than any other exogenous factor and is more important than endogenous lymphoglandular exacerbation. In this connection it also should be mentioned that tuberculosis among nurses in tuberculosis sanatoria was ten times as often observed by Ornstein and Meyerowitz (16) as in women working in various industries. To prevent exogenous infections and to isolate successfully its open sources will always remain the primary concern of any tuberculosis program. Nurses, medical students and physicians might very well be exposed for the first time to open cases of tuberculosis in sanatoria or from general hospital patients harboring specific lesions which are not recognized, and they remain exposed in the same environment also to repeated superinfections and perhaps in some instances to true reinfections. If careful analysis of postmortem material can point to the great importance of superinfection and reinfection, the practical social-hygienic value of such pathogenetic-morphological studies is by no means subordinated to their mere scientific interest.

That the views on the significant rôle of superinfection and (exogenous) reinfection in the pathogenesis of postprimary pulmonary tuberculosis, to some of which we have referred—with no pretense to completeness—are not shared by experienced clinicians and pathologists, here and abroad, is well known. According to Miller (17), the majority of active cases of pulmonary tuberculosis in the adult develop from previous lesions and not from exogenous reinfections. Ulrici (18) stresses the hematogenous involvement of the lungs from extrapulmonary lesions and also the importance of exacerbation of the original tuberculous infection within the primary focus. Hurwich and Milles (19), too, believe in the hematogenous nature of apical tuberculosis.

That chronic pulmonary tuberculosis is caused by further development of hematogenous metastatic lesions to the lungs from the primary tuberculous infection was the belief of Harbitz (2) and of Birch-Hirschfeld (2). Birch-Hirschfeld, in particular, pointed to the apical location of the beginning lesions

of pulmonary tuberculosis, caused by hematogenous spread from the old primary focus. This is also claimed by Huebschmann, according to whom most apical foci are hematogenous metastases. The proof for their hematogenous nature was believed to have been furnished by those cases examined by Huebschmann in which, postmortem, there were small tuberculous lesions in one or both apices, a more or less obsolete older primary complex, recent tuberculous meningitis, and "perhaps a few tubercles in the spleen." Our own material of fatal cases, part of which will be presented in one of the forthcoming papers, contains an anatomical observation similar to that of Huebschmann. We believe, however, that the anatomical analysis of our case will point to the exogenous nature of the apical lesions, and that Huebschmann's description of the more or less obsolete primary complex in his cases is a strong argument against the hematogenous nature of the recent apical tuberculous foci. Stefko is much more outspoken regarding the hematogenous nature of pulmonary tuberculosis. He declares all so-called "reinfections" to be hematogenous metastases of the primary complex.

In the preceding paper, the apical lesions in children, observed roentgenologically by Simon (20), were already referred to in their alleged relation to beginning pulmonary tuberculosis. They are, according to Simon, large nodular hematogenous tubercles formed during the active phase of primary tuberculosis; they might disintegrate and change into cavities. In one-third of the children with such apical lesions there was extrapulmonary tuberculosis. When these hematogenous apical nodules heal, they leave large calcified lesions which, according to Simon, are not uncommon in older children. Reinders (21), on the other hand, has called attention to the rare occurrence of these apical nodules in the post-mortem material of children below fifteen years of age, and we believe most pathologists will agree with Reinders in this respect.

Duken (22), as already stated in one of the preceding papers, questions the reliability of the roentgenological diagnosis in general as to the hematogenous character of these apical lesions, especially if found restricted to the site of the primary focus. Braeuning and Redecker (23), also, disputed the hematogenous nature of these foci isolated in the apices, while, on the other hand, they believe that to some extent early hematogenous dissemination into both lungs always happens in the active phase of the primary complex. To Loeschke (7) the roentgenological demonstration of some of Simon's clinical observations appeared to prove a gradual bronchogenic spread rather than a hematogenous one. Pagel (24), however, believed that the apical lesions as demonstrated by Simon are hematogenous metastases. While they might frequently initiate pulmonary tuberculosis (in 20 to 30 per cent), Pagel stressed, in accordance with Simon, the healing tendency of these apical hematogenous tubercles. The reinfections of Puhl are, in Pagel's opinion, hematogenous, because he has seen them twice as frequently in cases with hematogenous generalization as in those of isolated phthisis. The common pulmonary tuberculosis of the adult develops, according to Pagel, after the primary infection has healed without generalization. Then, "endogenous" reinfection originates in the revival of the old lesions in both

primary focus and lymph nodes. This Pagel has observed in 25 per cent of his postmortem material. In addition, progressive pulmonary tuberculosis caused by endogenous (meaning lymphohematogenous) metastasis was present in 20 per cent of all cases of tuberculosis of the lungs seen by Pagel. Views similar to these were stated by Wurm (25). He saw in the majority of cases of adult tuberculosis the result of a direct or indirect relapse of the primary focus. The "classical apical tuberculosis" related to "reinfection" and to apical scars is, in the majority, of hematogenous origin. Wurm admitted that pulmonary tuberculosis might develop also by contiguous involvement of the lung tissue from the active primary focus, within a relatively short time after first infection has taken place.

With this theory of revival or relapse or exacerbation of an old primary focus, which was held also by Stefko, Ghon, Beitzke and Schuermann disagreed insofar as they never had observed such an exacerbation when the primary focus had reached a fairly calcified state. Loeschke, in addition, denied that tuberculous lymph nodes with the specific lesions completely encapsulated, can furnish the source for hematogenous tuberculosis.

Regarding the relations between chronic pulmonary tuberculosis and fatal types of hematogenous tuberculosis, we are indebted to the systematic studies of Schuermann. From these we have learned that phthisis or intrabronchially spreading tuberculosis is much less marked and less acute in generalized hematogenous tuberculosis. This observation in itself should speak against the hematogenous nature of the usual picture of progressive pulmonary tuberculosis. The number of cases with fatal protracted hematogenous tuberculosis was about one-third of those of typical phthisis in Schuermann's material. On the other hand, the hematogenous dissemination seen in connection with and apparently secondary to chronic progressive pulmonary tuberculosis was of the chronic miliary and not of the acute overwhelming type.

Some references to the involvement of the bronchomediastinal lymph nodes in the different types of chronic pulmonary tuberculosis will be added in the following paper when this relationship is discussed on the basis of our own findings. For the present it might suffice to state that in Schuermann's postmortem material, in extensive tuberculous pulmonary processes there were always specific changes in the regional bronchomediastinal lymph nodes; also hematogenous tubercles in organs, such as kidneys, liver and spleen, were found in 50 to 60 per cent of such cases. This is in sharp contrast to Schmincke's (26) claim that in progressive pulmonary tuberculosis blood and lymph channels are practically closed to tubercle bacilli.

Our anatomical findings are arranged in table 1. In all of the 28 cases included in this paper, the tuberculous lesions were, as already mentioned, of incidental nature, even in the last case of our series, in which active progressive pulmonary tuberculosis in both lungs was found in connection with a typical older reinfection. The cause of death in this case was cancer of the stomach. Brief epicritic descriptions will be given of the tuberculous lesions in a few cases, especially in those selected for illustration. The original gross and

TABLE 1

*Anatomical findings in 28 cases of restricted pulmonary reinfection*

CASE NUMBER	AGE	RACE AND SEX	STATE AND SITE OF PRIMARY COMPLEX	NUMBER AND SITE OF REINFECTION FOCI	EXTENSION OF REINFECTION	VARIOUS ADDITIONAL OR SPECIAL FINDINGS
2122	40	White M	Single, firm, stony primary focus, 2 mm. in diameter, upper third, left upper. No lymph node lesions	Single, recent tuberculous lesion 3 mm. in diameter with early encapsulation, close and slightly anterior to the primary focus	None	Neither old nor recent changes in lymph nodes regional to both foci (serial sections)
2937	43	White M	Single, calcified ossified, pinhead-sized; lateral lower third, right upper	Single, 5 x 8 mm., chalky, calcified; between upper and medium third of left upper	None	Lymph nodes regional to right and left upper lobe negative in thorough gross and X-ray examination
2291	60	White M	Minute, ossified focus, upper third left lower. Firm calcification of a subpleural lymph nodule nearby	Lentil-sized, recent, caseated lesion; close to the ossified lesion (mistaken grossly for nonspecific lesion)	None	All bronchopulmonary and tracheobronchial lymph nodes regional to the left lung negative (serial sections)
2781	42	Colored M	Single, stony ossified state; lower third, left lower. No corresponding lymph node changes (serial sections)	Single, walnut-sized, caseated chalky focus in each subapical field, on the right side 3 cm., on the left side 5 cm. below apex. Centro chalky, periphery firmly caseated	A few microscopical epithelioid giant cell tubercles in several lymph nodes of the left upper tracheobronchial group	Note the microscopical lymphogenous progression from the left subapical reinfection, and the absence of a complex change to the primary focus
2202	63	White F	Two firm, stony complexes with three foci in the right and seven in the left lung; all stony and in part ossified	Fibrous-chalky nodule in right apex, about hazelnut-sized	Localized tuberculous hyperplasia in one right interlobar lymph node regional to right apex	Few hematogenous tubercles in the left kidney
2112	48	White F	Primary focus, 2 mm., in stony ossified state; upper third right lower. Minute calcified splinters in one regional bronchopulmonary lymph node	Single focus, 1.3 x 0.8 cm., firmly caseated, with little chalky change; between upper and middle third, left upper	None	Lymph nodes regional to left lung negative
2052	49	White M	Single firmly calcified, ossified, pinhead-sized; base right lower. Few hyalinized conglomerate tubercles in regional bronchopulmonary lymph nodes	Single, about 8 x 3 mm., in subapical field of left upper, in chalky fibrous state	None	Lymph nodes draining left lung entirely negative (histological control)
4952	43	Colored M	Single, minute, firm, stony, ossified focus; hilar level right upper, with firm stones in regional bronchopulmonary and upper tracheobronchial lymph nodes	Two, firmly chalky fibrous and fibrocaseated, about 3 to 5 mm., with slight calcification in one of them, in apical area of right upper	None	No recent lesions in the lymph nodes regional to the right lung

TABLE 1—*Continued*

CASE NUMBER	AGE	RACE AND SEX	STATE AND SITE OF PRIMARY COMPLEX	NUMBER AND SITE OF REINFECTION FOCI	EXTENSION OF REINFECTION	VARIOUS ADDITIONAL OR SPECIAL FINDINGS
2078	61	White M	Pinhead-sized calcified focus; middle third left lower, with firm calcification of three regional bronchopulmonary lymph nodes	Two pea-sized, chalky and firmly caseated, in hilar level of right lung (lower part right upper and upper third right lower)	None	Lymph nodes regional to right lung negative
4683	63	White F	Minute, firmly ossified focus; lower part right upper. Firm stony tubercles in regional right bronchopulmonary group	Single, cherry-sized, wedge-shaped in lower anterior part of right middle lobe, completely caseated, surrounded by recent conglomerate tubercles. No lymphogenous spread	Distinct perifocal spread	Near each apex, one minute, firm, stony focus (old superinfection or focal extension?). No histological study of these two stony apical lesions
2076	71	White M	Two ossified complexes with three ossified stony foci in lower part right upper and in right middle lobe, and two stony foci in lower part left upper. Stony changes in two regional lymph node groups on both sides	Single, firmly anthraxotic, calcified, well encapsulated, wedge-shaped, about 1 x 0.5 cm.; left apex	None	Old localized reinfection in area drained by lymph nodes of one of the primary complexes
E-121	52	White M	Three stony, ossified primary foci; left upper, below hilar level and subapical. Minimal complex changes in one interlobar bronchopulmonary lymph node	A few pea-sized caseated fibrous, chalky tubercles about 3 cm. below left apex	None	None
3398	44	White F	Single pea-sized calcified focus; lower third right lower. Massive calcification of all regional tracheobronchial lymph nodes, extending to paratracheal on same side	Two slightly larger caseated chalky, subapical area of right upper, near mediastinum	None	None
3105	69	White M	Single, pea-sized, ossified primary focus; base right lower. Ossification of regional bronchopulmonary and lower tracheobronchial lymph nodes	Several scattered fibrous calcified and large chalky lesions, varying from 1 to 10 mm. in diameter, restricted to both apical and subapical areas	Restricted apical and subapical localization. No lymphogenous progression from the reinfection	None

TABLE 1—Continued

CASE NUMBER	AGE	RACE AND SEX	STATE AND SITE OF PRIMARY COMPLEX	NUMBER AND SITE OF REINFECTION FOCI	EXTENSION OF REINFECTION	VARIOUS ADDITIONAL OR SPECIAL FINDINGS
2167	78	White M	Two stony, ossified complexes, each primary focus firmly ossified, hemp-seed-sized; upper part right lower, upper third left upper. Regional bronchopulmonary lymph nodes on both sides calcified	Single, small cherry-sized, caseated, encapsulated lesion in right subapical area. Nonspecific scar in left apex	None	None
3300	57	White F	Two pinhead-sized, ossified-stony primary foci in base and upper third right lower, with firm calcification of regional bronchopulmonary lymph nodes	Several chalky fibrous caseated tubercles; subapical area of right upper and upper third of right lower, largest lesion 8 mm. in diameter	Restricted localized spread to upper part of right lower lobe	No tuberculous lesions in lymph nodes closest to right subapical area
2246	61	White F	Primary focus stony ossified; middle third left upper, 6 mm. diameter. Firm calcification of four regional lymph node groups	Single, large pea-sized, caseated pneumonic focus in fibrous encapsulation; left subapical area	Localized spread in left subapical area with a few recent conglomerate tubercles around the reinfection focus, spreading close to the level of the primary focus; also a few recent tubercles in right apex	No recent tuberculous lesions in the lymph nodes draining the left upper lobe. Old hyaline tubercles in capsule of liver
2103	61	White M	Single primary focus, stony; hilar level left upper, with firm calcification of bronchopulmonary and upper tracheobronchial lymph nodes	Single in medium third right upper, 1 cm. in diameter, with central cavitation, in caseated state and beginning organization	A few recent and a few older caseated fibrous, conglomerate tubercles around the reinfection focus; mostly perifocal spread	Lymph nodes regional to right upper negative
2275	41	White M	Single, lower third right upper, about 3 mm., in firm stony state, partly ossified. Firm calcification of regional bronchopulmonary and upper tracheobronchial lymph nodes	Several chalky caseated, partly calcified tubercles; subapical field right upper, the largest bean-sized with central cavitation	Localized spread to apex and through subapical field with several cheesy fibrous lesions and recent caseation in typical peribronchial arrangement	No recent lymph node changes regional to the entire right lung. Left lung free
4722	70	White F	Lentil-sized, calcified ossified focus; lower third right lower, with stony changes in regional lower tracheobronchial lymph nodes	About eleven well encapsulated fibrous, caseated tubercles from 3 to 6 mm. One large one, 1 x 1.5 cm. near right apex	All eleven tubercles scattered over both lungs, including the lower lobes near the pleural surface. Lesion in right apex shows slight central chalky changes	No lymphogenic extension from reinfections. Apparently restricted focal aspiration from right subapical to different parts of both lungs. No hematogenous lesions



TABLE 1—*Continued*

CASE NUMBER	AGE	RACE AND SEX	STATE AND SITE OF PRIMARY COMPLEX	NUMBER AND SITE OF REINFECTION FOCI	EXTENSION OF REINFECTION	VARIOUS ADDITIONAL OR SPECIAL FINDINGS
3257	56	White M	Two lentil-sized, stony ossified foci; base right lower. Firm stony tuberculosis of regional bronchopulmonary lymph nodes, hilum right lower	Moderately extensive calcified and chalky bronchial and peribronchial, in part pencil-like changes in left apex and subapical field; older caseated lesions in right apex	Typical localization in apex and lateral subapical field of the left and central and lateral subapical field of the right upper lobe	No lymph node changes regional to upper lobes. Distinct ossification in some apical lesions of left upper
2733	71	White M	Single, pinhead-sized primary focus, stony, ossified, medium third, left lower. Firm calcification of all regional lymph nodes	Typical multiple firmly calcified and distinctly ossified tubercles, rather densely arranged	In typical location: left subapical area and right apical and subapical area	No calcification of lymph nodes regional to right lung. Extensive bone formation in apical and subapical lesions (apparently very old reinfection or superinfection)
4787	56	White M	Single pinhead-sized in firmly calcified ossified state in right middle lobe. One calcified regional upper tracheobronchial lymph node	Nodular, fibro-caseated lesions in left apical and subapical area, about 4 x 3 cm., with hazelnut-sized cavity	Small nodular lesions also in subapical area right upper, with pen-sized cavity and recent scattered peribronchial tubercles in both lower lobes	Histological combination of older fibrous with very active caseation. No lymphogenous spread from reinfection lesions. No hematogenous seeding
3305	52	White M	Single pinhead-sized, firmly calcified; base right lower; firm calcification of right lower tracheobronchial and two subpleural lymph nodes in right lung	Multiple, firmly chalky calcified and fibrous lesions symmetrically in both apical and upper subapical areas	Restricted to subapical fields	No lymph node changes regional to upper lobes (Case not examined histologically; very typical X-ray picture)
4833	27	White F	Pinhead-sized, firmly calcified single focus; mid-portion right upper. Firm calcification of regional bronchopulmonary and upper tracheobronchial lymph nodes	Densely arranged multiple cheesy-chalky tubercles in left apex and subapical field	A few recent peribronchial cheesy tubercles in the left lower lobe	Superinfection or reinfection. (No histological examination)
2333	64	White F	Single, minute ossified with stony centre, hilar level right upper. Small calcified splinters in regional bronchopulmonary lymph nodes	Single, hazelnut-sized in chalky calcified state; right upper, subapical field, 4 cm. below apex	A few caseated, fibrous tubercles with chalky centers, arranged closely around the focus	Intrapulmonary lymph node regional to reinfection shows extensive silicosis with localized chalky fibrous nodules
2144	55	White M	Firmly calcified complex, lentil-sized primary focus; lower third right upper. Stones in regional bronchopulmonary and anterior mediastinal lymph nodes	A few irregular small fibrous and calcified lesions below left apex, with hyaline conglomerate tubercles in regional bronchopulmonary lymph nodes	Restricted to apex and immediate subapical area of left upper, with lymphogenous spread to regional bronchopulmonary lymph nodes	Additional firm caseated focus in middle third right upper. Left subapical lesions in part ossified; in right upper, cheesy fibrous. No lymphogenous spread from the latter

TABLE 1—*Concluded*

CASE NUMBER	AGE	RACE AND SEX	STATE AND SITE OF PRIMARY COMPLEX	NUMBER AND SITE OF REINFECTION FOCI	EXTENSION OF REINFECTION	VARIOUS ADDITIONAL OR SPECIAL FINDINGS
2547	62	White M	Minute calcified ossified focus in left lower, and extensive stone formation in two regional bronchopulmonary and lower tracheobronchial lymph node groups	Distinct, fibrous-chalky tuberculosis in right lateral subapical field, extending into apex and lower part of right upper lobe. Small, calcified and fibrous conglomerate tubercles in bronchopulmonary and upper tracheobronchial lymph nodes regional to right upper lobe	From right upper lobe to left lung; with recent tuberculous bronchopneumonia; midportion left upper and a few small scattered areas in left lower	Hyaline calcified tuberculosis in one subpleural lymph node of right middle lobe

histological protocol of all tuberculous findings in each case is very detailed. The few case reports given below are condensed abstracts of the individual summaries ("epicrisis") attached to all cases examined in our studies on human tuberculosis.

#### CASE REPORTS

*Case 1:* (B.G.H. 2122) Forty year old white male. Cause of death: acute pancreas necrosis. (Plate 1)

There is a firm, calcified focus, 2 mm. in diameter, in the upper third of the left upper lobe, 6 cm. below the summit. A second small, grayish lesion is found at the same level, very near to the anterior surface, grossly appearing more like a softened subpleural lymph nodule. All lymph nodes draining the left upper lobe are negative, both grossly and according to the roentgen film. The right lung is entirely free.

All bronchomediastinal lymph nodes draining the left lung, including the bronchopulmonary, tracheobronchial and paratracheal groups, were examined in serial sections. Neither old nor recent tuberculous lesions were found.

The primary focus has the typical histological structure of an old stony lesion, with a firm, calcified centre encased within a complete bony ring which, in turn, is attached to a rather thin hyaline capsule laden in some areas with anthracotic pigment. The soft subpleural nodule proved at histological examination to be a fairly recent tuberculous lesion, microscopically of lobular pneumonic character, restricted to an area of 2 to 3 mm. in diameter. It has a distinctly caseated centre. The entire lesion actually consists of two confluent bronchiolar tubercles showing slight encapsulation with epithelioid cells. There is some nuclear debris in the centre surrounded by firm, fibrinous pneumonic exudate which, in turn, is lined by epithelioid cells, some of which are changing into fibroblasts. The surrounding moderately anthracotic parenchyma contains a rare epithelioid cell tubercle.

Plate 1 shows location and size of the old primary and the recent reinfection tubercle. Neither the old nor the recent infection had produced any spread to lymph nodes. Except for these two lesions, there were no tubercles seen, neither in any other part of the lung nor outside of the lungs.



PLATE 1

*Case 2:* (B.G.H. 2291) Sixty year old white male. Cause of death: carcinoma of the sigmoid.

In the upper third of the left lower lobe there is a minute, firmly calcified, and—in the histological picture—considerably ossified primary focus, with a great part of the stony centre resorbed by lymphoid marrow. A nearby intrapulmonary lymph nodule is completely hyalinized. One subpleural nodule at the interlobar surface of the left upper lobe about at the level of the primary focus, has a firmly calcified centre within a broad hyaline capsule. All lymph nodes draining the left lung were examined in serial sections. Only in one lymph node of the bronchopulmonary group, at the hilum of the left lung, there were found a few hyaline scars, one of them nodular.

A small grayish, relatively minute lesion, close to the primary focus, grossly of non-specific appearance, was also examined. It proved to be a relatively recent tuberculous caseated focus with minimal fibrous encapsulation, with a great deal of nuclear debris in the centre and with a few, in part hyalinized, epithelioid cell tubercles near the periphery of the focus. The incomplete hyaline capsule is surrounded by a few small caseated tubercles. The right lung and all its regional lymph nodes are entirely free of tuberculous lesions.

Here, then, we are dealing with an entirely incidental finding of a relatively recent reinfection, hardly larger than a small lentil, at the level of an old ossified typical primary focus. There was no gross evidence of further spread of this reinfection in the lungs.

*Case 3:* (B.G.H. 4683) Sixty-three year old white female. Cause of death: pyelonephritis. (Plate 2)

This is a most characteristic case of a closed stony complex with a minute primary focus in the lower part of the right upper lobe near the hilum. Histologically it shows beautifully preserved osseous structures containing a great deal of bone marrow and small remnants of calcified stony detritus attached to the bony shell. In two areas this bony shell has apparently been entirely resorbed, allowing a direct communication of the surrounding fibrous tissue with the marrow. In each apex there is also a minute calcified lesion, the X-ray appearance of which likewise points to bone formation. (These two latter lesions, in quite symmetrical position, have not been examined histologically.) The reinfection is presented by a wedge-shaped lesion about the size of a cherry, in the lower anterior mediastinal area of the right middle lobe. This focus appears in a caseated state, slightly firm, and completely encapsulated, with perfectly preserved alveolar pneumonic pattern. It is surrounded by many small, recently caseated conglomerate tubercles with typical tuberculous granulation tissue, including Langhans' giant cells. There are a few emphysematous alveoli included in these granulations. In other nearby areas there are a few small fibrous scars, surrounded by Langhans' giant cells. The progression of tuberculosis into the surrounding area is more pronounced than was expected from the gross appearance. Part of the attached lung tissue shows considerable atelectasis.

This is a text-book picture of an old primary complex and of a relatively recent active reinfection.

The lymph nodes draining the area of the reinfection in the right middle lobe are negative.

*Case 4:* (B.G.H. 2103) Sixty-one year old white male. Cause of death: carcinoma of the esophagus.

There is a typical primary calcified complex, with the primary focus in firm, stony



PLATE 2

state, 0.5 cm. beneath the anterior surface slightly above the hilar level of the left upper lobe, with distinct calcified changes in the regional bronchopulmonary and upper tracheobronchial lymph nodes.

In the lateral portion of the right upper lobe between upper and middle third there is a hazelnut-sized grayish focus with minute central cavitation surrounded by a few small grayish tubercles. All lymph nodes draining the right lung are negative.

The primary focus is completely calcified and for the most part surrounded by a bony shell. Part of the lung tissue around this focus shows considerable fibrosis and anthracosis. All lymph nodes regional to this focus show huge stony conglomerate tubercles, fairly well encapsulated, and a few smaller hyalinized tubercles but no active tuberculous lesions.

The reinfection focus is still in a caseated state with unusually marked necrobiosis, especially near the border which shows ingrowing fibrous tissue in connection with a thin collagenous wall. Very close to the focus there are recent caseated tubercles along with older conglomerate tubercles with central caseation and hyalinization along the border. There is also active tuberculous granulation tissue between these smaller tubercles with many Langhans' giant cells. It seems as if this focus of reinfection had brought about a locally spreading tuberculosis of fibrocaseated nature, but, in part, with still recent tubercles. The lymph nodes regional to the right upper lobe were entirely negative.

*Case 5: (B.G.H. 4787)* Fifty-six year old white male. Cause of death: myocardial infarct.

There is a typical stony complex with a pinhead-sized primary focus in firmly calcified state, partly ossified, and surrounded by a rather thick hyaline capsule. Only one lymph node in the regional upper tracheobronchial group contains a few calcified, hyalinized tubercles. (In close proximity to the primary focus there is a small silicotic nodule.) The reinfection is characterized by a very typical nodular tuberculosis, mostly in fibrous and somewhat fibrocaseous state in the subapical portion of the left upper lobe, with a cavity of about hazelnut-size, and by small, fibrocaseous lesions with a minute cavity in the right upper lobe.

The histological picture of the reinfection lesions shows a combination of older fibrous tuberculous changes with very active caseation, and here and there small anthracosilicotic nodules between the fibrocaseous tubercles. There is no evidence of tuberculosis in any lymph nodes draining the upper lobes on both sides, but distinct effects of aspiration to the lower lobes, with recent bronchial and peribronchial tubercles.

*Case 6: (B.G.H. 2937)* Forty-three year old white male. Cause of death: purulent peritonitis. (Plate 3)

This is an apparently typical case of single focal reinfection in the presence of an old healed primary focus in the opposite upper lobe. No X-ray nor gross evidence of complex formation is seen on either side. The primary focus is pinhead-sized, completely calcified, located in the lateral lower third of the right upper lobe. The reinfection focus, considerably larger than the primary focus, is in chalky-calcified state, between upper and middle third of the left upper lobe, of somewhat more irregular shape but firmly encased within a hyaline capsule.

The histological picture of the primary focus shows (in the decalcified section) a beautifully preserved alveolar pneumonic structure with a complete bony wall and very firm calcification. The histological picture of the focus of reinfection shows a massive, firmly caseous-chalky central area and an unusually broad hyaline band, also localized



PLATE 3

bud-like protrusions of this capsule containing some firm chalky matter. The calcification is much less marked, presenting firm, chalky detritus rather than stone formation. The reinfection is obviously already in a well established state of chalky-calcified regression.

It is of interest to note in this case that neither the firm stony focus in the right lung nor the obviously less old reinfection focus in the left lung had produced any lesions in the lymph nodes draining these areas which could have been noticed by X-ray or by careful gross inspection. These lymph nodes were not examined histologically, so it is impossible to state whether or not microscopic scars or tubercles might have been present as the sole remnants of a complex formation.

*Case 7: (B.G.H. 2112)* Forty-eight year old white female. Cause of death: acoustic nerve tumor; brain swelling. (Plate 4 with the X-ray film and microphotographs. The primary focus was cut in two before the X-ray picture was taken.)

There is a stony primary complex with the primary focus about 2 mm. in diameter in the upper third of the right lower lobe, and with a very minute calcified splinter in one right bronchopulmonary hilar lymph node. In the lateral part of the left upper lobe, 8 cm. below the apex, between upper and middle third, there is an about bean-sized, encapsulated, chalky focus. In the lymph nodes draining the left lung neither chalky nor caseated lesions are found but only moderate anthracosis. The primary focus is histologically typically built, showing a firm stony centre with a thin bony shell inside a relatively thin hyaline wall. There is irregular fibrosis of the lung tissue firmly attached to the capsule of the primary focus. There are two firmly hyalinized, conglomerate tubercles in the regional right bronchopulmonary lymph nodes, the larger of which contains some calcified detritus. The lymph node process is not that of firm stone formation, but rather of extensive hyalinization with firmly encased calcified-chalky material. The large reinfection lesion has a very typical structure: firm caseation with relatively slight chalky changes with firm encapsulation of the entire focus; in some areas of the centre there are cholesterol needles and also some disintegrating caseated debris. This lesion appears focally restricted. There are no tuberculous changes found in the lung tissue surrounding this reinfection lesion. All the lymph nodes draining the left lung were histologically examined and found to be entirely free of tuberculous changes.

*Case 8: (B.G.H. 4722)* Seventy year old white female. Cause of death: pulmonary thrombo-embolism. (Plates 5a and 5b)

There is a calcified primary complex with a lentil-sized focus in the right lower lobe and with calcification of the regional lower tracheobronchial lymph nodes. A second single, pinhead-sized, subpleural calcified focus in the upper third of the right upper lobe, about 5 cm. below the dome in the lateral portion proved, at histological examination, to be a silicotic nodule.

The reinfection lesions included: a localized, grayish, fibrous tuberculous lesion 1 to 1.5 cm. in diameter, in the apex of the right upper lobe, somewhat wedge-shaped, with a hemp-seed sized, chalky tubercle slightly below this area; several well encapsulated, cheesy-fibrous tubercles throughout both lungs, numbering eleven altogether, and varying in size from a pea to a hazelnut, most of them near the pleural surface.

The bronchopulmonary lymph nodes above the right bronchus at the mediastinal surface of the right upper lobe and between right upper and right middle lobes show firm anthracosis but no calcification. There is no evidence of hematogenous tuberculosis anywhere.





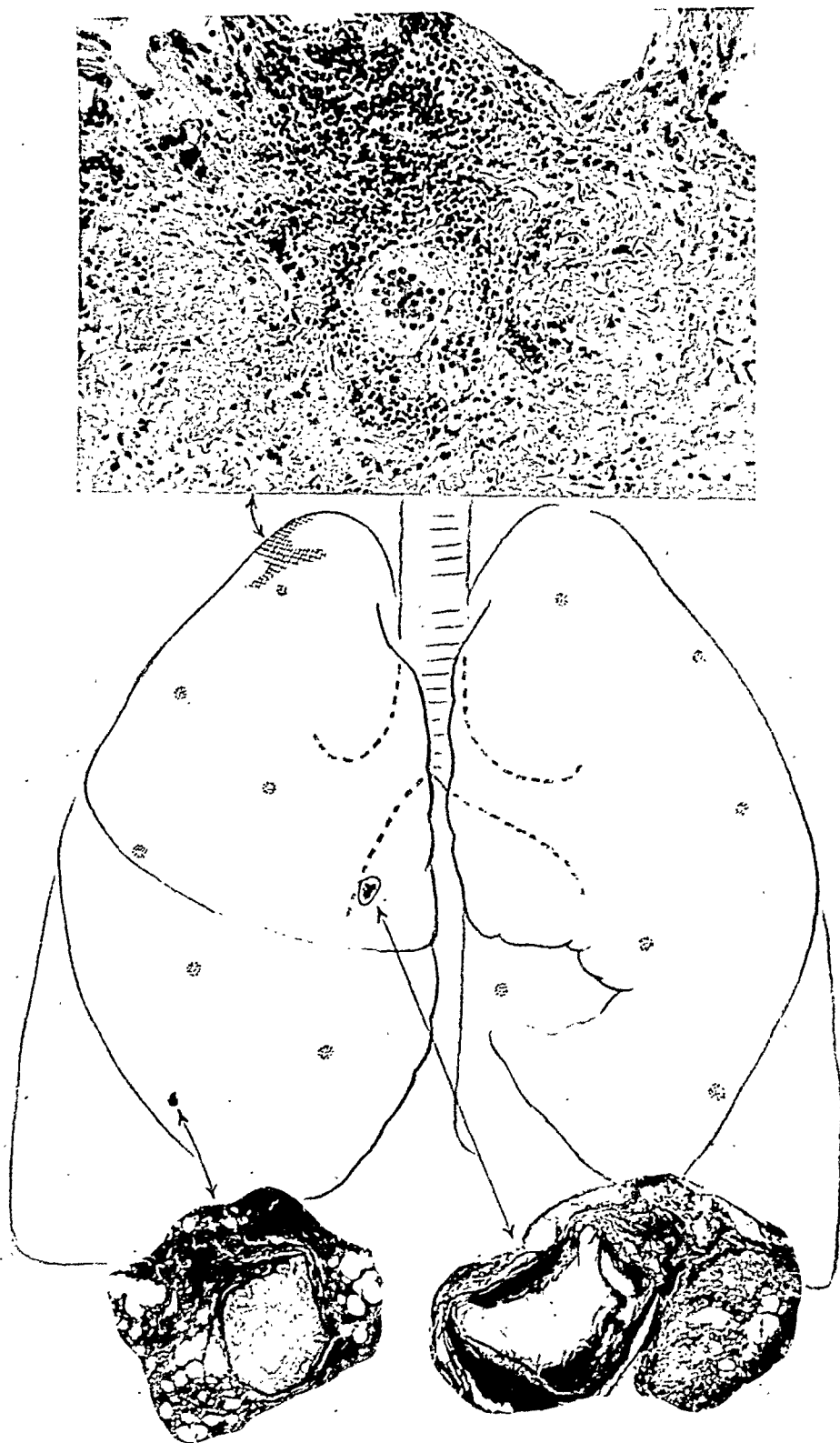
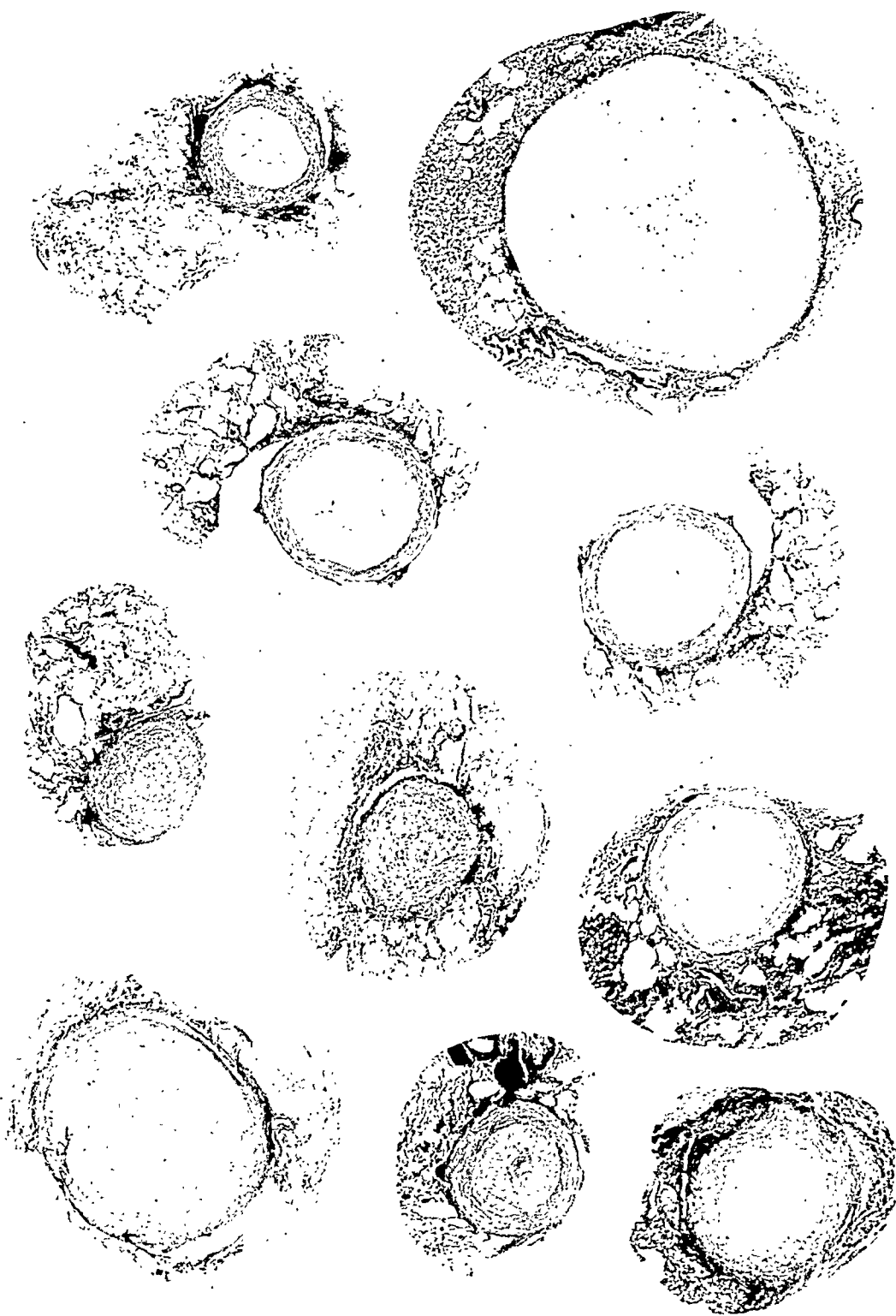


PLATE 5a

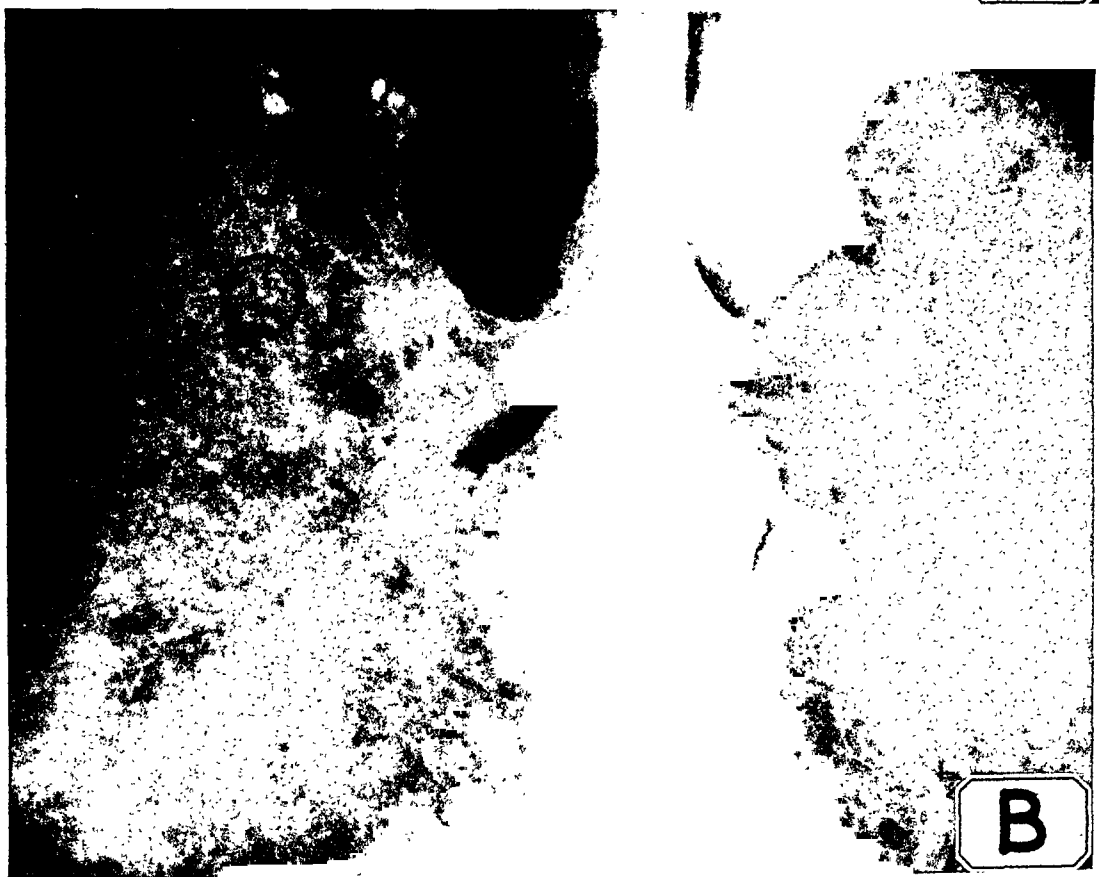
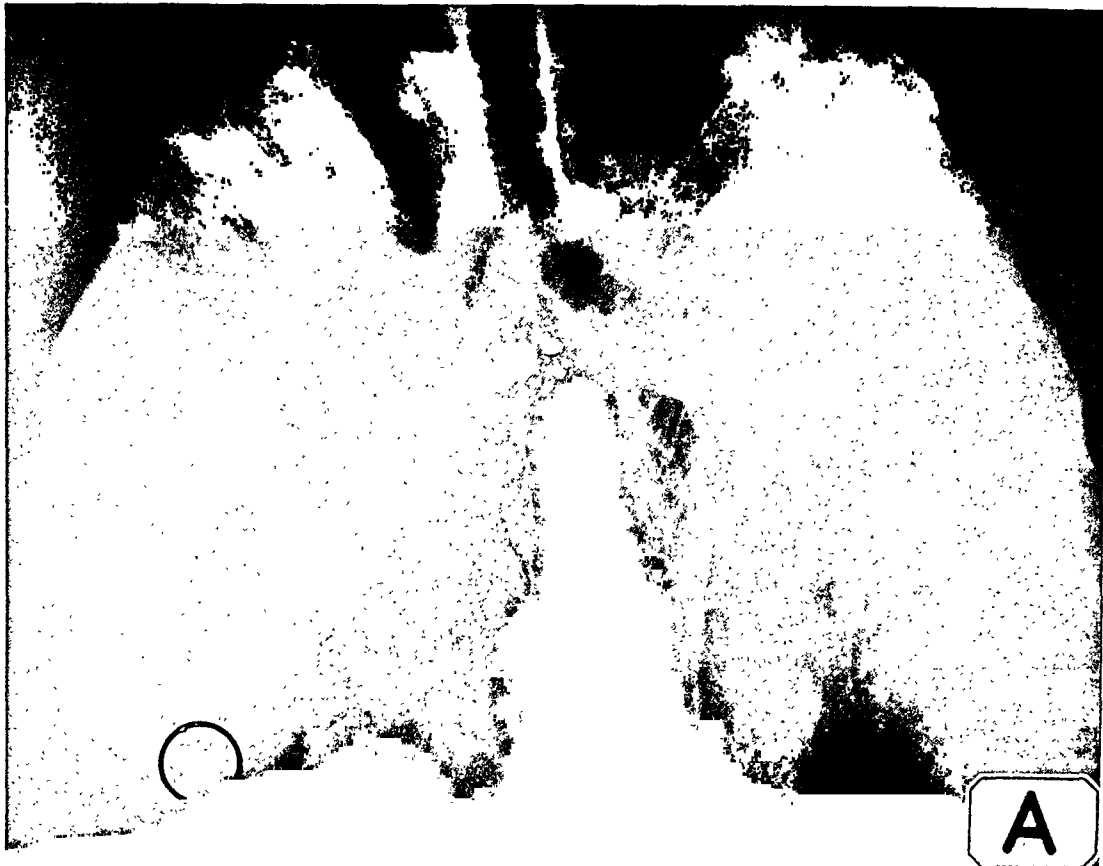


The X-ray picture does not indicate any calcium in these scattered tubercles in both lungs (except for a minimal trace in one subapical tubercle in the right upper lobe below the apical scar.) The caseated tubercles vary from 3 to 6 mm. in diameter. All of them show, histologically, a perfectly preserved alveolar pneumonic, firmly caseated pattern and are surrounded by concentric collagenous fibres. The scar in the right apex shows collapse-induration, with moderate edema, with a few slightly ectatic bronchi included in the atelectatic area. Only in one angle of this scar there are a few Langhans' giant cells. It seems as if we were dealing here with obturation atelectasis following occlusion of a nearby bronchus by a firm fibrous-chalky tubercle which was clearly seen in the X-ray photograph. Along the periphery of the scar there are, in several areas, small epithelioid and giant cell tubercles surrounded by lymphocytes, very close to typically emphysematous alveoli along the border of the indurated area.

This, then, is a typical case of an old calcified complex with the primary focus encased by a firm bony capsule and with distinct stones in the regional lymph nodes closest to the primary focus, combined with scattered lesions of fairly recent reinfection, possibly originating from a fibrous-chalky subapical tubercle, to various parts of both lungs. These scattered tubercles, though well encapsulated, are for the most part still in a caseated or cheesy-fibrous state. They are not in a genetic relationship to the entirely obsolete osseous, stony complex. There was no lymphogenous progression from the various reinfection lesions and especially no endogenous reactivation in the lymph nodes regional to the primary focus. All tubercles in connection with the reinfection lesion had the same histological structure.

A fairly typical X-ray picture of bilateral apical and subapical reinfection lesions is represented on plate 6, A (see case 3105 in table 1). Note the faint grayish ring around the central compact white core in the old primary focus. The ring corresponds to the bony shell, the whitish centre to firm stony matter, the intervening, somewhat translucent space to bone marrow between the central stone and the ossified ring. The regional lymph nodes contained very firm, compact and fragmented stones with distinct ossification. The reinfection lesions consisted mostly of small, fibrous-calcified splinters and chalky caseated tubercles, the largest of which measured 10 mm. in diameter. The massive shadow in the right lower lobe corresponds to recent nonspecific pneumonia and atelectasis. (This patient died from a perforated duodenal ulcer.)

Photograph B on the same plate represents a unilateral localized apical reinfection of the right lung. The importance of microscopical analysis of all shadow-producing lesions is clearly demonstrated in this instance. Preceding histological analysis, it was not clear whether or not the calcified changes in the right bronchopulmonary and upper tracheobronchial lymph nodes were tributary to the apical lesions. Only complete histological analysis of all chalky and calcified lesions clarified the relationship of the various parenchymatous lesions to each other and to the firmly calcified lymph nodes. It disclosed a typical primary complex with a single, distinctly ossified-stony focus in the lower part of the right upper lobe (encircled on the photograph); both regional lymph node groups contained very hard, stony conglomerate tubercles. Of the apical lesions, appearing as grayish white and whitish, somewhat irregularly shaped patches, the lateral focus was in firmly caseated but slightly chalky state and represented a pulmonary peribronchitic tubercle. The medial whitish shadow was caused by soft chalky changes in an intrapulmonary lymph nodule with minimal anthracosilicosis. Structurally these apical lesions appeared of a more recent age than the firmly ossified-stony complex. (This patient died from a recent coronary thrombosis with massive heart infarct.)



## DISCUSSION

A comparative analysis of the number, extent and anatomical state of activity of the lesions of reinfection, as listed in table 1, reveals the following facts: With the exception of one case (no. 2246) in which a few hyalinized tubercles were found in the capsule of the liver, there were, in not a single case of the entire series, no hematogenous tubercles present anywhere, which could have been related to the old primary complex. In the exception mentioned, the complex changes regional to the old primary focus involved four lymph node groups. The lesions brought about by the reinfections were in most instances considerably restricted. Lymphogenous progression from the area of the focally restricted reinfections was minimal and of only microscopic dimensions. It was seen in 2 cases only. In one of them there were a few epithelioid giant cell tubercles in several lymph nodes regional to a walnut-sized reinfection lesion in one subapical area. In the other, the lymphogenous progression had led to tuberculous hyperplasia of one interlobar lymph node regional to a fibrous-chalky lesion in the right apical area. This latter is the only case in the entire series in which a few recent hematogenous tubercles were seen (in one kidney), apparently of metastatic nature, caused by the localized lymphogenous spread from the reinfection lesion.

Gross tuberculous changes in lymph nodes regional to the lesions of reinfection were present only in 2 cases, the last included in our series (no. 2144 and no. 2547 in table 1). In one of them the reinfection had extended from the right subapical area throughout the entire right upper lobe and to both lobes of the left lung. But only the lymph nodes regional to the area of the original reinfection in the right subapical field contained several older conglomerate tubercles.

That the changes designated as reinfection could not have been formed in any other way than by a new exogenous infection is clear from the entire anatomical picture and from a structural comparison between the primary focus and the lesion or lesions caused by the reinfection. In all cases the primary focus and the tuberculous changes in the regional lymph nodes were in a firmly calcified and in part ossified, obsolete state. The picture in the lesions of reinfection varied considerably in the individual cases. In 6 instances it was still in an active state, in some of these with signs of localized extension around the reinfection focus. In others there were various phases of firmly caseated or caseous-chalky regression with fibrous encapsulation and minimal or more marked central calcification. In a few cases (such as no. 3257 and no. 2733) some of these subapical tubercles were in part ossified. It is in these and a few similar cases with firm stony and old fibrous calcified lesions, in which no decision can be made as to the question of superinfection or true reinfection responsible for the old subapical lesions. In the majority of our cases, however, especially in all those instances in which the reinfections were single or very few in number, their structural age was clearly below that of the old obsolete primary complex. These, we feel, represent the anatomical substrate of true, restricted reinfections.

As to the number of the reinfection lesions, they were, macroscopically, dis-

tinctly single in 12 cases. In 4, there were two reinfects close together, and in 6 other cases there were several scattered reinfection lesions. All of these were restricted to one apical and subapical area. Only in 5 out of the total of 28 cases included in this series, were the upper portions of both upper lobes the site of the reinfection lesions. The scattered distribution of several reinfection lesions of both lungs was unusual (in case no. 4722, plate 5) suggestive of focal aspiration or extension from a fair sized reinfection in the right subapical area. In this case, too, there was no genetic link whatsoever between the firm, stony, ossified primary complex and the reinfection lesions. Incidentally, in 2 cases (no. 2167 and no. 4952) an entirely caseated or caseous-chalky intrapulmonary lymph nodule was found close to the focus of reinfection; on the X-ray film and grossly this had been mistaken for a second reinfection lesion.

The location of the reinfection lesions in the 28 cases was as follows: left upper lobe, 9; right upper lobe, 9; both upper lobes, 7; right middle lobe, 1; hilar level of right upper and right lower lobe, 2. In the few cases listed in table 1, in which different parts of both lungs were involved by the extending reinfection, the oldest reinfection lesions were clearly of focal character and of apical or subapical location.

The size of the single or—in some instances—of the clearly older focal subapical lesions differed from 3 to 13 mm. in diameter. Most of the measurements in the individual protocols represent diameters of ellipsoid structures. These varied from 3 to 5 mm. to 8 to 14 mm. Other sizes given included variations from a lentil to a cherry or walnut. In the few cases with several subapical tubercles, their sizes varied from 2 to 10 mm. in diameter.

It was believed by Aschoff and Puhl (3) that there is always a clear structural distinction between the primary focus and the reinfection lesions. In the primary focus the outer capsule surrounding the calcified stone or the bony shell was found considerably thinner by Puhl than in the so-called reinfects. It is the thickness of the so-called outer capsule which was considered characteristic of the reinfection lesion. Puhl, in addition, pointed out some other diagnostic criteria of the "reinfect" and its structural distinction from the primary focus, especially in later stages of regression. These focal lesions of reinfection are, according to Puhl, more polymorph, not as round as the primary foci, or again, oblong with a cord-like calcified or chalky axis. The collagenous capsule is very broad and is, as a rule, surrounded by a firm anthracotic, indurated area. Although Puhl has stated that firm calcification in the centre of these reinfects is rare, he has added that with increasing age calcification naturally becomes more marked, and that eventually complete stone formation and ossification will replace the caseated or chalky-fibrous lesions of reinfection.

Plates 7 and 8 give some additional illustrations of the structural distinction between primary foci and apical or subapical reinfection lesions. These slides were selected at random from 4 cases of our series. "B" designates the primary focus, "A" the reinfection lesion or lesions. (On the right half of plate 7, figure B should be designated as A, and figure C should be designated as B.) Note the comparatively small size and fairly round shape of the primary foci on plate 7 (E. H. 121, and 3257), while in the lower field of plate 8 (2246) the primary focus shows

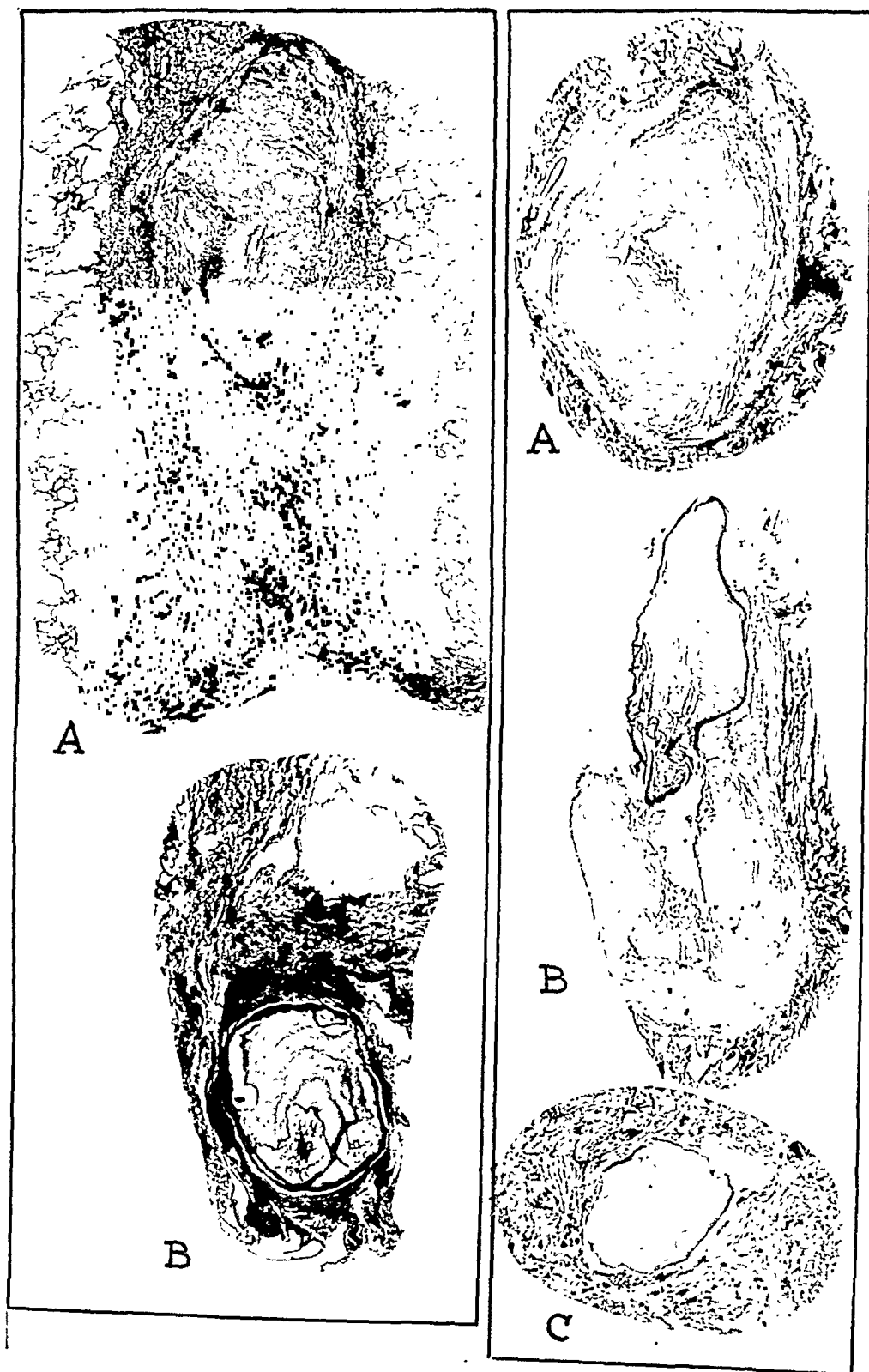
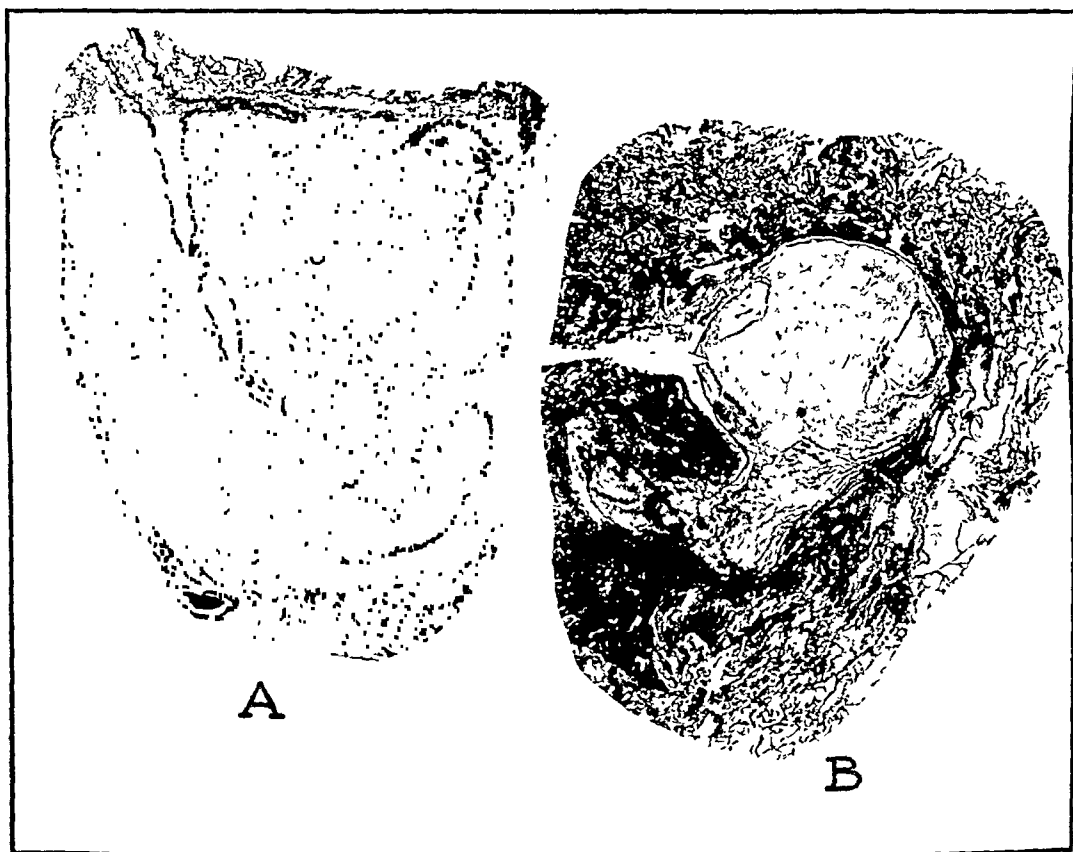
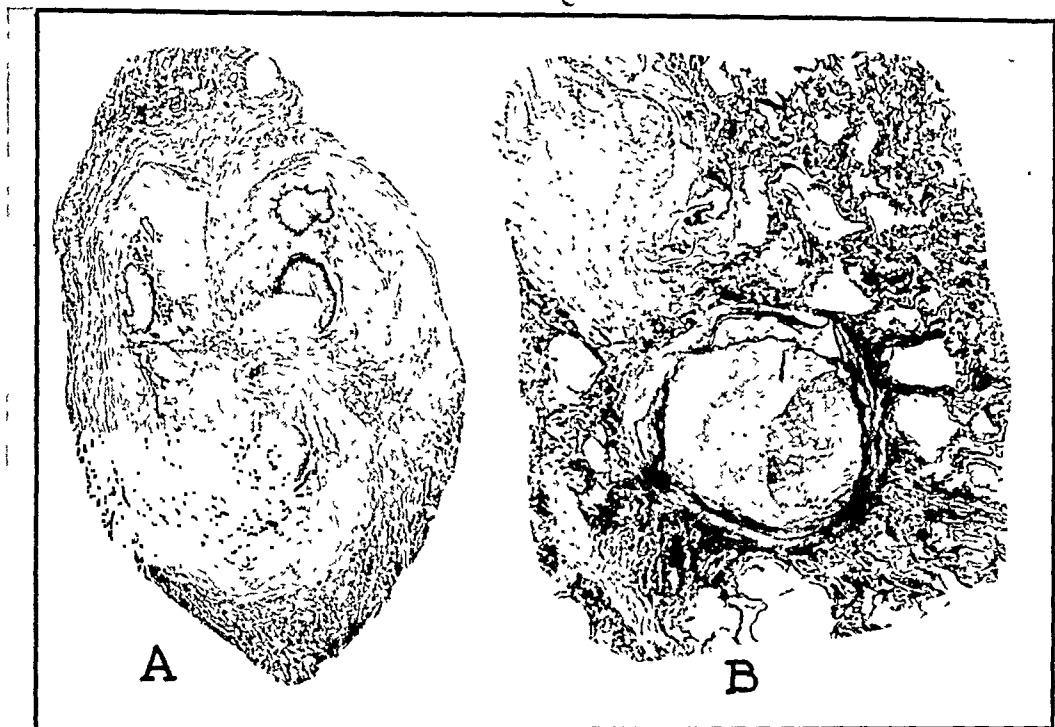


PLATE 7





an irregular, finger-like extension with hyaline scar tissue attached to the bony capsule; the alveolar pneumonic structure is faintly noticeable in the core of the focus in the van Gieson-elastica preparation. The primary focus in the upper field of plate 8 (2202) shows also a scar-like structure attached to a small segment of its capsule. Part of its stony substance is resorbed by bone marrow, as it is, to even a more marked degree, in the primary focus on plate 7 (E. H. 121).

In the reinfection lesions the ovoid and oblong shape is well seen in both cases on plate 7 and in the upper field (2202) on plate 8. This shape and pencil-like, chalky or stony structures, encased within fairly thick fibrous walls, point to the original intrabronchial location and to intrabronchial extension of these reinfection lesions. The massive focal atelectasis between the pleura and one reinfection lesion seen on plate 7 (E. H. 121) points in the same direction. That the wall of some "reinfects" is relatively thin can be noticed in the uppermost picture to the right on plate 7 (3257), and in the large, relatively recent caseated pneumonic reinfection lesion (elastic tissue stain) from case 2246, in the lower field of plate 8. A rather impressive picture of irregular calcification, leading to small, bizarre shaped, stony fragments within organizing hyaline scar tissue, surrounding some caseated and chalky detritus, is shown in the upper field of plate 8 (2202); it represents a chalky fibrous reinfection lesion from the right apex.

Some of the criteria given by Puhl are present in a few of the reinfection lesions in our own cases, especially in those in which the "reinfect" was of distinctly larger size than the primary focus. An oblong shape, a small central cavity containing caseated chalky detritus with cholesterol crystals, or—in older lesions—pencil-like chalky-calcified central cords, rather massive collagenous hyalinization of the capsule which was found to be of considerable thickness, or, in other instances, more irregular and less conspicuous fibrosis of the wall and occasionally nodular hyaline protrusions of the thick hyalinized capsule, all this could be observed in a few of the restricted focal reinfection lesions. In all these cases the primary focus was in the typical obsolete, stony-ossified state and of the usual small size. On the other hand, in a few cases included in our series, there seemed to be no clear difference in the thickness of the capsules between primary and reinfection lesions, and especially not in those cases in which primary focus and "reinfect" were of approximately the same size. Also, considerable scarring around the primary focus and rather irregular thickening of its capsule could be observed in a few primary lesions. In fact, in one instance the capsule around the reinfection focus, which was in a state of moderately advanced regression, was considerably thinner than the capsule of the primary focus. There is, we feel, no exclusive diagnostic criterion of the so-called "reinfect" of Puhl. Large primary foci, for instance, in various phases of regression, cannot be distinguished by their histological structure alone from reinfection lesions of similar size. This question, however, has in general little practical significance. The lesions of reinfection are frequently multiple, the primary focus usually single and associated with the corresponding lymph node—complex changes. If, however, primary focus and tubercles formed by

exogenous superinfection or reinfection are within the same apical or subapical area of one upper lobe, restricted to a relatively small field, drained by the same lymph node chain, and if all these lesions are examined in a later state of calcified or ossified regression, it might be impossible to recognize any lesion as the true primary focus. We believe, then, that Puhl's description fits primarily those lesions of reinfection which are distinctly larger than primary foci and which, in addition, show the effects of localized perifocal spread. The structural distinction between primary and reinfection lesions, if present at all, is more of a quantitative nature, depending on the difference in the volume of the lesions. Therefore, it is understandable that Frimann-Dahl (27) has found it sometimes difficult to distinguish, on the structural basis alone, between so-called reinfects and primary foci, that Kalbfleisch found some lesions of reinfection of entirely similar structure to that of primary foci, and that Loeschke does not at all believe in any structural distinction between primary focus and focal lesions of reinfection.

The location of the restricted lesions of exogenous reinfection given in our tables is nearly the same as that reported by Puhl and Schuermann; our own figures are surprisingly close especially to those of Puhl. In Schuermann's material, 87 per cent of all postprimary lesions, thought to be exogenous superinfections, were from 2 to 5 fingers below the apex within the upper portions of one or the other upper lobe. McPhedran's (28) experience appears in line with these anatomical observations when he states that the origin of adult tuberculosis is always in the upper third of the lung.

Finally, we wish to call attention to the fact that in 2 cases (no. 2122 and no. 2937 in table 1) the primary lesion and the lesion of reinfection were restricted entirely to the lung tissue, without leading to any further involvement of the nearby regional lymph nodes. In both cases, all lymph nodes regional to the area of the primary focus and the reinfection focus were entirely negative on thorough gross and roentgenological examination, in one of them supplemented by complete serial sections. This can be interpreted as a successful resistance of the host tissue, sufficiently effective to localize primary and reinfection to their original site in the lung. The size of the primary focus and of the reinfection focus was not smaller than seen in other cases with typical complex formation. It is of no less interest to observe that, while the primary infection might be restricted to the parenchymal focus, localized reinfection might show lymphogenous progression, if only of microscopical nature, as in no. 2781, the fourth case listed on table 1.

#### SUMMARY

The anatomical and histological picture of true exogenous reinfection, presented for the most part by lesions few in number or single, is described on the basis of complete morphological analysis in 28 cases. In all, the reinfection lesions were found incidentally postmortem and were of no clinical significance. In all, there was a typical old primary complex present, with the primary focus and the corresponding regional lymph node lesions in a completely obsolete state, and with no sign of exacerbation in either the focus or the lymph nodes.

There was no trace of old hematogenous tubercles anywhere, including the lungs, which could have been formed at the time of the first infection. In the absence of any complicating sequelae beyond the old, obsolete complex, the exogenous nature of the subapical and apical reinfection lesions appeared beyond doubt in these cases. In a good number of instances their recent, caseated state, with localized perifocal progression, pointed to true reinfection. In others, with several lesions in typical subapical location, the state of advanced fibrocalcified or—rarely—ossified regression did not permit decision as to whether or not the primary complex was already healed when the new exogenous infection had occurred. In all cases presented, the postprimary subapical tubercles are the results of new infections from without, exogenous reinfections or superinfections. Their histological structure, as compared with that of the primary focus, is briefly discussed. Certain structural variations, especially in regard to the thickness of the capsule around the primary focus and the so-called “reinfect” (Puhl), are considered to be merely quantitative differences—dependent on the volume of primary and reinfection lesion, respectively, but not as specific diagnostic structural distinctions. The location of the restricted reinfection lesions was in most instances in the upper third of one upper lobe, and only in a few exceptional cases in the right middle lobe and at the hilar level of the right lung.

The strict meaning of the term “reinfection,” referring exclusively to new infections from without, is restated, and the various views on the nature of the “reinfection,” as given in the more recent literature especially in relation to the pathogenesis of so-called adult tuberculosis, are cited and critically analyzed.

#### SUMARIO

Tomando por base el completo análisis morfológico de 28 casos, describíse el cuadro anatómico e histológico de la verdadera reinfección exógena representada en su mayoría por lesiones ya aisladas o escasas. En todos se encontraron las lesiones de reinfección fortuitamente en la autopsia y carecían de importancia clínica. En todos había un típico complejo primario antiguo presente hallándose el foco primario y las correspondientes lesiones de los ganglios linfáticos regionales en un estado completamente anticuado y sin signos de exacerbación ni en el foco ni en los ganglios. Tampoco había indicios de antiguos tubérculos hematógenos en ninguna parte, incluso los pulmones, que hubieran podido formarse al tener lugar la primera infección. A falta de secuelas complicantes aparte del viejo complejo anticuado, la naturaleza exógena de las lesiones subapicales y apicales de reinfección parecía indudable en esos casos. En un buen número de ellos el estado caseado reciente con evolución perifocal localizada, denotaba verdadera reinfección. En otros, con varias lesiones en típica situación subapical, el estado de regresión fibrocalcificada o raramente osificada, avanzada, no permitía decidir si el complejo primario estaba ya cicatrizado cuando tuvo lugar la nueva infección exógena. En todos los casos presentados, los tubérculos subapicales postprimarios constituían el resultado de nuevas infecciones del exterior: reinfecciones o superinfecciones exógenas. Discútese

sucintamente su histología comparada con la del foco primario. Considéranse como diferencias meramente cuantitativas ciertas variaciones histológicas, sobre todo con respecto al espesor de la cápsula que rodeaba el foco primario y al llamado "reinfecto" (Puhl), dependientes del volumen de las lesiones primarias y de reinfección, respectivamente, pero sin constituir distinciones histológicas diagnósticas específicas. La localización de las lesiones limitadas de reinfección quedaba en la mayor parte de los casos en el tercio superior de un lóbulo superior y sólo en algunos casos excepcionales en el lóbulo medio derecho y al nivel hiliar del pulmón derecho.

Reexpresase el significado preciso del término "reinfección," limitándose exclusivamente a infecciones nuevas procedentes del exterior, y cítanse y análizanse críticamente las varias teorías de la naturaleza de la "reinfección," tal como se expresa en la literatura más reciente, en particular en relación con la patogenia de la llamada tuberculosis del adulto.

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## BOOKS

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By THE STAFF OF WM. H. MAYBURY SANATORIUM  
(Henry Stuart Willis)

The reviewer of a book does well to scrutinize the preface or foreword, for here the author often gives the cue to the aim and scope of the work. In the foreword of the book under review, Doctor Rafferty has told his aims. He states that pneumothorax is too often a term applied without critique and without standards; that the book stresses the utter need of standards, the importance of strictly defining indications and contraindications, the seriousness of complications and the prevention of the latter. He has called attention to the fact that his book does not discuss technique but places emphasis upon the usefulness of pneumothorax when applied intelligently and as a part of a general collapse therapy program.

Thus the book is not a manual for beginners: rather it is a treatise on the basic principles that should undergird the physician practicing pneumothorax. It is written for the man in the field of tuberculosis who should know his technique. It is concerned, therefore, not with technique but with judgment and with the physician's basic understanding of tuberculosis and collapse problems. It evaluates pneumothorax as it fits into the sanatorium regimen and the general scheme of collapse therapy.

The book is divided into three parts: (1) General Considerations, (2) Choice of Cases and (3) Management. It discusses collapse measures in tuberculosis and indicates the integration of pneumothorax into the scheme. It emphasizes the obligatory use of pneumonolysis in many cases and points out the indications for primary thoracoplasty without a trial at pneumothorax. In particular it stresses factors leading to complications and states that the latter should be few indeed if indications and contraindications are kept in mind (and this would include indications for discontinuing pneumothorax as well as those for beginning it). It calls attention to tuberculosis of the tracheobronchial tree and brings a new and stimulating story of this type of tuberculosis, particularly as it concerns a collapse program. It gives a clear-cut discussion of the tension cavity and, in general, offers the student of tuberculosis a great deal of "food for thought."

One of the main points of emphasis concerns the uses and abuses of pneumothorax. Many people still reckon all patients as having therapeutic pneumothorax if air is injected into their chests. The space may be large or small, free

NOTE: The review of this book which was published in the November, 1944 issue of THE AMERICAN REVIEW OF TUBERCULOSIS has caused considerable discussion and protest by correspondence. We are, therefore, glad to print this second review which presents a totally different evaluation than did the first one. [EDITOR]

or adherent, wet or dry, recent or old: pulmonary cavity may be open, closing, closed or blocked: sputum may be positive or negative—all this is called pneumothorax, analysis of which has given and continues to give the most bizarre results. It is precisely this protean thing called pneumothorax that Doctor Rafferty has revealed in his book and has tried to clarify. For this he has sought to establish standards. He calls for criteria, lays down indications and contraindications and pleads against (often fatal) prolongation of inadequate pneumothorax.

In this book the author puts in bold relief the value of short term "exploratory pneumothorax," which, if practiced widely, would cut deep into the harvest of complications. "The ability to make an early decision as to the effectiveness or estimated effectiveness of pneumothorax is one of the most valuable assets the phthisiologist can possess." Most people of experience in this branch of medicine will agree with this statement. Since there is no unanimity of opinion on pneumothorax, it would be silly to expect all to agree with all of Doctor Rafferty's concepts. Yet presentation, discussion and criticism of them cannot but advance our knowledge.

It should be pointed out that the author has not written a text-book which would include technique and clear delineation of all the features of pneumothorax, including the pathology and pathological physiology of the collapsed lung. Rather than a text-book, it is a contribution to a changing field of thought in medicine.

Readers of this review may take exception to the fact that it emanates from the institution where Doctor Rafferty has lived and worked and obtained his background in tuberculosis—that, in other words, our review would be prejudiced. This may well be true, but it has been made in order to present what the reviewers believe to be the kernel of the book. And it has been done because we feel that Doctor Rubin's review of this book in the November, 1944 issue of the REVIEW failed to capture the aim, motive and, to a great extent, the content of the book, or at least failed to convey it to the reader.

Our position seems fair in the circumstances. In fact, several recognized authorities in tuberculosis have written commendatory letters to the author and more than twenty favorable reviews of the book have appeared. Hence our effort in bringing the book further to the attention of readers of THE AMERICAN REVIEW OF TUBERCULOSIS.

## AMERICAN TRUDEAU SOCIETY

### Report of the Committee on Policy

Dr. Chesley Bush, *Chairman*

Dr. John Alexander

Dr. J. Burns Amberson, Jr.

Dr. James J. Waring

The American Trudeau Society indorses the principle that physicians specializing in tuberculosis, or other restricted branches, should be fundamentally well qualified in internal medicine. This is the principle also underlying the policies of the American Board of Internal Medicine in certifying specialists. The American Trudeau Society coöperates with the American Board of Internal Medicine to this end. The Society encourages and urges its members who are interested in becoming certified, to apply to the American Board of Internal Medicine. The proper procedure is as follows:

The applicant must first be certified in internal medicine by the American Board after he has satisfied the requirements and has passed written and oral examinations. After such certification he may apply for additional certification in the subspecialty of tuberculosis. On passing an oral examination in the subject of the subspecialty, he may then receive this additional certification by vote of the American Board of Internal Medicine. Request for formal application blanks and for other information should be addressed to Dr. William A. Werrell, Assistant Secretary-Treasurer, American Board of Internal Medicine, 1301 University Avenue, Madison 5, Wisconsin.





# PULMONARY ALVEOLAR ADENOMATOSIS IN MAN<sup>1,2</sup>

Is This the Same Disease as Jaagsiekte in Sheep?

DAVID A. WOOD<sup>3</sup> AND PHILIP H. PIERSON

Pulmonary alveolar adenomatosis is a rare disease in man. Less than a dozen authenticated cases have been reported. In the literature there appear the cases of Löhlein (1), Sims (2), Oberndorfer (3), Helly (4), Bonne (5), Richardson (6), Briese (7), Bell (8) and Taft and Nickerson (9). The human disease is of particular interest not only because of its obscure etiology, alleged rarity and little understood pathogenesis, but because of its remarkable resemblance to a benign pulmonary adenomatosis (*Jaagsiekte*) occurring epizootically in the sheep of certain widely scattered parts of the world—in South Africa, Iceland, Montana and England. In such localities it is commonly believed that the disease is infectious and capable of epidemiological spread. In Iceland, pulmonary adenomatosis (epizootic adenomatosis) has been responsible for severe economic losses. According to Dungal (10) some farms have lost 50 to 85 per cent of their flocks due to this disease which, insofar as can be determined, made its first appearance in Iceland in 1934.

Diagnosis in all human cases to date has been established only on material obtained at the autopsy table. Recently, we have had the unique opportunity of studying a case in which the diagnosis was established as a consequence of lobectomy six months prior to death. While under observation, our patient subsequently developed an adeno-acanthoma of the cervix and, at autopsy, also showed bizarre metaplastic changes in the kidney, pancreas and thyroid gland. It is our opinion that the uterine cancer developed independent of the multicentric adenomatous pulmonary lesions. Not only because of the fact that this is the first case diagnosed antemortem, but because an opportunity has been afforded for the study of a possible virus etiology, this case is reported at this time, in the hope of stimulating further interest and observations in similar cases.

## CASE REPORT

Our patient was a widow, fifty-seven years of age, who had been employed as a telephone switchboard operator. For the preceding two years she had complained of fatigue, night sweats and cough. When first seen in March, 1942 she presented the above complaints and stated that the cough had been productive at times of a small amount of whitish sputum. There had been occasions when the sputum had been not only brownish

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<sup>2</sup> This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

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but blood tinged. In the ensuing year dyspnea upon exertion had become noticeable. The patient stated that six weeks prior to the onset of her present illness she had had a chill and a bout of fever which had been diagnosed by her family physician as due to gallbladder disease. Neither the family nor the past history revealed anything of importance contributing to the present illness. She stated that she had always lived an urban existence and at no time had been associated with farming or with animals. Physical examination revealed a well developed and nourished but tired woman. Aside from her lungs no abnormality was noted. In the right axilla there was slight dulness with showers of subcrepitant râles, but no change in breath sounds. The blood pressure was 150 systolic over 90 diastolic. Laboratory studies of blood, urine and sputum were uniformly negative. An X-ray film of the chest taken April 1, 1942 showed an oval thin-walled cavity in the axillary region of the right lower lobe, and an indefinite annular shadow in the upper mesial portion of the same lobe. The other lobes were essentially normal (figure 1). On February 20, 1943, the following year, an X-ray film of the chest showed the right lower lobe to appear shrunken and dense. The cavity in the upper portion had persisted and was more clearly outlined than it had been previously (figures 2 and 3).

Bronchoscopy was performed April 27, 1942. No abnormality was noted except that pus was seen coming from the lateral branch of the right lower lobe bronchus. Cultures from this material showed staphylococcus albus and nonhemolytic streptococci. After consultation with Dr. Emile Holman, it was agreed that operative drainage of the cavity should be performed, and this was done May 2, 1942. At operation the pleural surfaces were smooth and free of adhesions. Upon palpation the lower lobe appeared to be free of disease. In spite of the roentgenogram of the chest, Doctor Holman concluded that the cavity was draining satisfactorily through the bronchus and pneumothorax treatment was instituted.

The patient's weight during her first stay in the hospital dropped from 126 pounds to 111 pounds. By the end of July, it rose gradually to 115 pounds and the patient felt better. There was still some cough but very little sputum. Nevertheless, the cavity previously suspected in the upper part of the right lower lobe appeared to be quite definite but thin-walled. After discontinuance of the pneumothorax, the patient was readmitted to the hospital. On July 9, Doctor Holman again explored this lobe. What seemed to be adhesions between the visceral and parietal pleura were so insecure that during the operation they gave way. The abscess cavity was incised, and, after swabbing out some gray pus, a mushroom catheter was fixed in place. Sulfanilamide powder was instilled into the wound which was then closed tightly. In spite of the fact that the catheter came out in six days the cavity had closed, and in the ensuing month her cough and expectoration had become negligible. Her weight rose gradually to 120 pounds. Weight gain continued during the fall and winter of 1942 so that by February, 1943 she weighed 135 pounds. When seen in February, 1943, there was some cough and a small amount of whitish sputum. The latter had a faint, nonoffensive odor. By the middle of February her sputum had increased to about 100 cc. daily.

Following fluoroscopy and X-ray films on February 20, it was agreed that in view of the unsuccessful treatment of the cavities by pneumothorax the right lower lobe should be removed. A preliminary bronchoscopy at this time did not show any granulation tissue or tumor in the bronchi. Lobectomy was performed on February 27, accompanied by crushing of the right phrenic nerve. Only a few adhesions were found in the region of the second operation.

Gross examination of the removed lobe (43S186) revealed multiple small grayish tumors of miliary size. Prior to its receipt in the laboratory the lobe had been fixed in 10 per cent

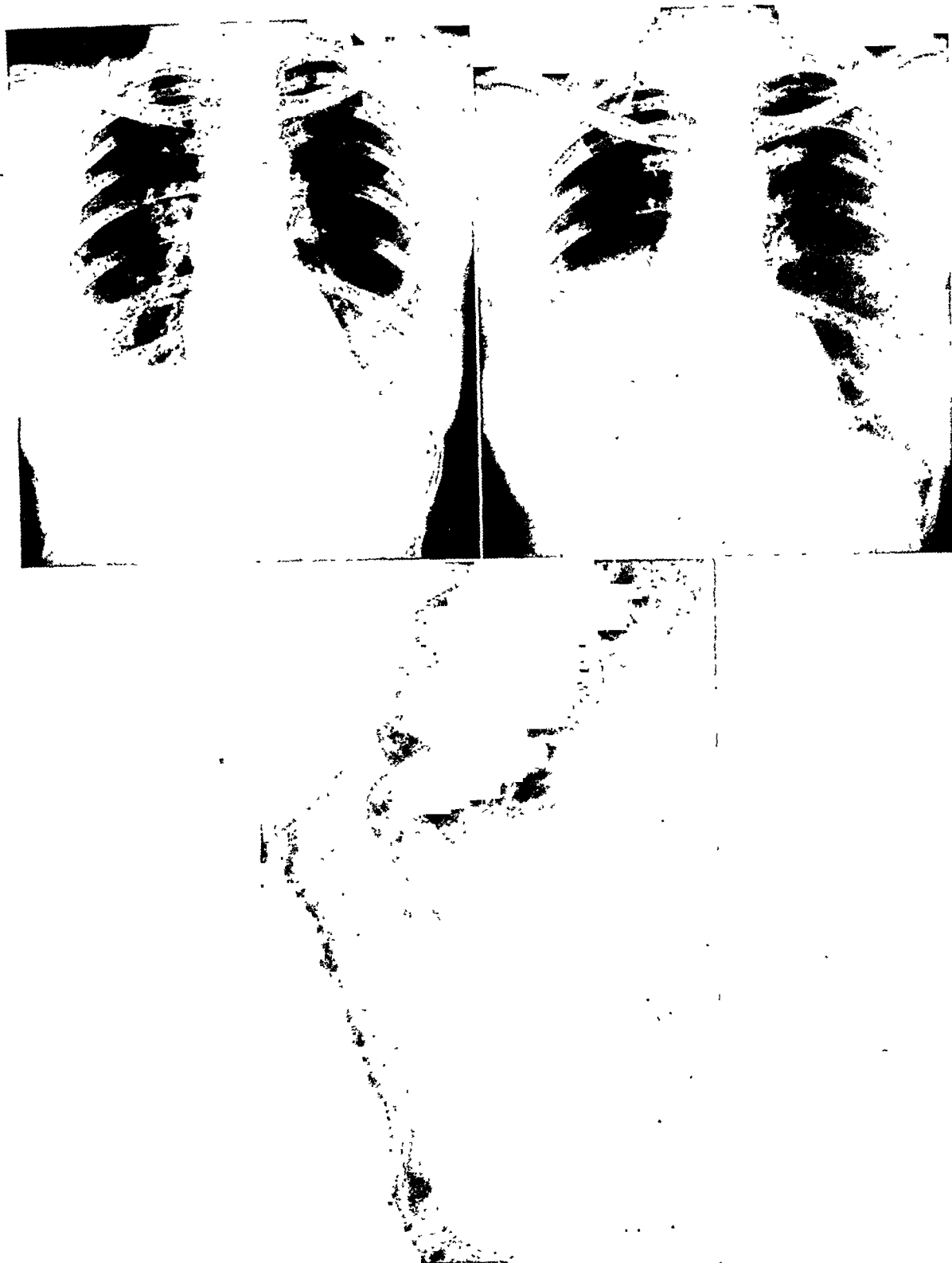


FIG. 1. (Upper left) Film of chest taken April 1, 1942 shows oval, thin-walled cavity in axillary region of right lower lobe and an indefinite annular shadow in the upper mesial portion.

FIG. 2. (Upper right) Chest film taken February 20, 1943. The right lower lobe appears shrunken and dense. It will be noted that the cavity in its upper portion has persisted and is more clearly outlined than previously (see figure 1). A close-up view of the right lower lobe is shown in figure 3.

FIG. 3. (Bottom) Right lower lobe. February 20, 1943. Note the clear outlines of a cavity in the upper mesial portion of the lobe. The rest of the lobe appears shrunken and dense.

formalin. The weight of the lobe was 356 g. Aside from a few filmy fibrous adhesions over the upper portion, the pleura was smooth. The lung tissue was firm and only slightly crepitant. It was firmest at the upper pole. A small amount of frothy fluid was contained in the bronchus. Upon cutting, a thin-walled cavity was found near the apex of the lobe; it measured 2.0 cm. in width. The surrounding parenchyma was studded by a myriad of closely grouped white nodules which averaged 0.1 cm. in width. Many were

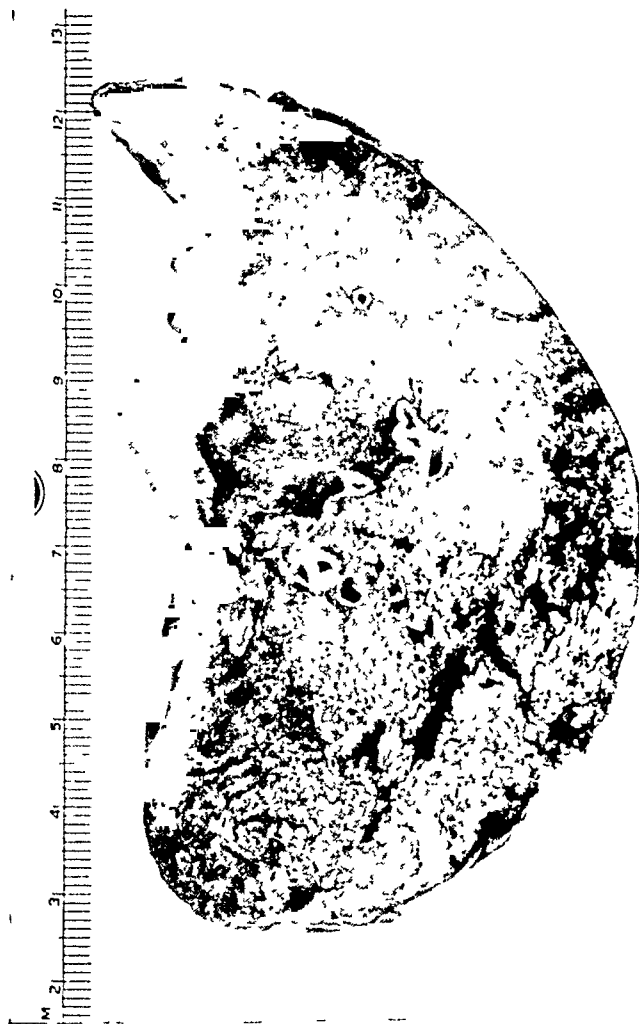


FIG. 4. Lobectomy specimen. Cross section of formalin fixed right lower lobe. Note the myriad of tiny white nodules, resembling somewhat the appearance of miliary tuberculosis. (The irregularity in the lateral portion of the lobe is an artefact due to tearing.)

coalescent. Toward the base they became less numerous. The appearance presented was somewhat that of noncaseating miliary tuberculosis (figure 4).

Histologically, all sections (taken from various representative portions of the lobe) showed a striking hyperplasia of columnar epithelial cells which focally lined various alveoli (figure 5). These foci showed varying degrees of proliferation with the formation of intraalveolar papillary and cystadenomatous masses of columnar cells (figure 6). In places a single row of columnar cells lined the alveoli. In all areas careful study revealed

apparent preservation of the alveolar stroma. The cells varied from low to tall columnar and were nonciliated. Their cytoplasm was finely granular and moderately eosinophilic. Occasional cells showed nuclear inclusion bodies. Quite uniformly, the nuclei were pale, presenting finely reticulated chromatin. Although a majority of the nuclei were basal in position, many were mesially placed. Mitotic figures were extremely infrequent. In the areas of slightest involvement the only change present seems to be that which involved the epithelium. No inflammatory or stromal changes existed in such areas (figure 7). In larger areas, however, small numbers of loosely scattered lymphocytes and plasma cells occurred in the stroma. There was also a mild perivascular collaring by similar cells. No apparent relationship existed between the inflammatory foci and the masses of hyperplastic alveolar cells. Occasional, otherwise normal alveoli contained desquamated septal cells, mononuclear phagocytes and very occasional polymorphonuclear leucocytes. In none, however, was there fibrin or definite exudate. Sections of the peribronchial lymph nodes showed a moderate deposition of anthracotic pigment, but no tumor cells. Adjacent bronchioles showed no papillary or proliferative changes of their lining epithelial cells. Contained within their lumina was a mucinous substance which contained not only occasional mononuclear phagocytes but also moderate numbers of columnar epithelial cells. These had the appearance of desquamated epithelial tumor cells. The uniformity of the cells, absence of recognizable stroma invasion, and the absence of metastases were interpreted as strongly indicative of a multicentric benign papillary proliferation of alveolar lining cells, most probably epithelial. The histological diagnosis on the above lobectomy specimen was: "Adenomatosis, lung, papillary, diffuse (alveolar)."

*Postoperative course:* During the first six weeks following lobectomy, the patient's course was favorable. She was free of fever, ambulatory, and showed no loss of weight. Sputum had ceased and dyspnea seemed to be decreasing. A chest film taken April 15, 1943, six weeks postoperatively, showed clear lung fields, free of demonstrable disease. The high diaphragm on the right was secondary to the lobectomy (figure 8). The patient remained quite well until May at which time she developed a slight cough, expectoration and increased dyspnea. She also noticed some vaginal bleeding for the first time. This was investigated and a biopsy showed an adeno-acanthoma of the uterine cervix (figure 9). This was treated by radium applied to the lesion and by X-ray treatment to the pelvis. Because the patient complained of pains in her back and legs, X-ray films of the pelvis and spine were taken. These showed an area of bone destruction in the right ilium and a tiny area in the body of the fourth lumbar vertebra. Thereupon, the patient was hospitalized. Because it was evident that the carcinomatous disease was spreading rapidly, continuation of X-ray therapy was attempted, some being administered to the chest. So much nausea and discomfort resulted that it was eventually discontinued. During the patient's stay in the hospital she was markedly short of breath, even without exertion. Her temperature rarely went over 100°F. and her pulse varied between 110 and 130. X-ray films of her chest taken July 23, 1943 showed some scattered infiltrations throughout both lungs which had previously been clear. Much of this new infiltration was on the right side in the upper and middle lobes. The patient progressively became worse and expired on August 26, 1943.

*Autopsy:* Necropsy was performed two and one-half hours after death. The body was that of a slimly built, emaciated woman who appeared to be about sixty years of age.

No fluid nor adhesions were found in the left pleural cavity. Numerous easily broken fibrous adhesions subtotally obliterated the right pleural cavity, being most numerous between the lung and the right leaf of the diaphragm. The pulmonary artery contained fluid blood. It was cannulated *in situ*, and, observing sterile technique, 1,000 cc. of sterile



FIGS. 5-7

normal saline solution was perfused rapidly through the lungs. In so doing it was noted that the saline solution passed through the pulmonary capillary bed at a surprisingly rapid rate. (Keeping the lungs sterile, representative portions of each were pooled into two groups and kept for animal studies. One group was frozen in carbon dioxide snow and the other placed in a solution consisting of equal parts of physiological saline and glycerine.)

The left lung weighed 450 g. It possessed a small subapical pleural scar. The pleura over each lobe was dotted by a number of "icing-like" grayish white, oval areas of thickening. These were widely scattered and measured up to 1.0 cm. in diameter. A small amount of yellow fibrin covered the diaphragmatic pleura as well as the visceral pleura over the lateral aspect of the lower lobe. The freshly cut surface of the lung was brownish



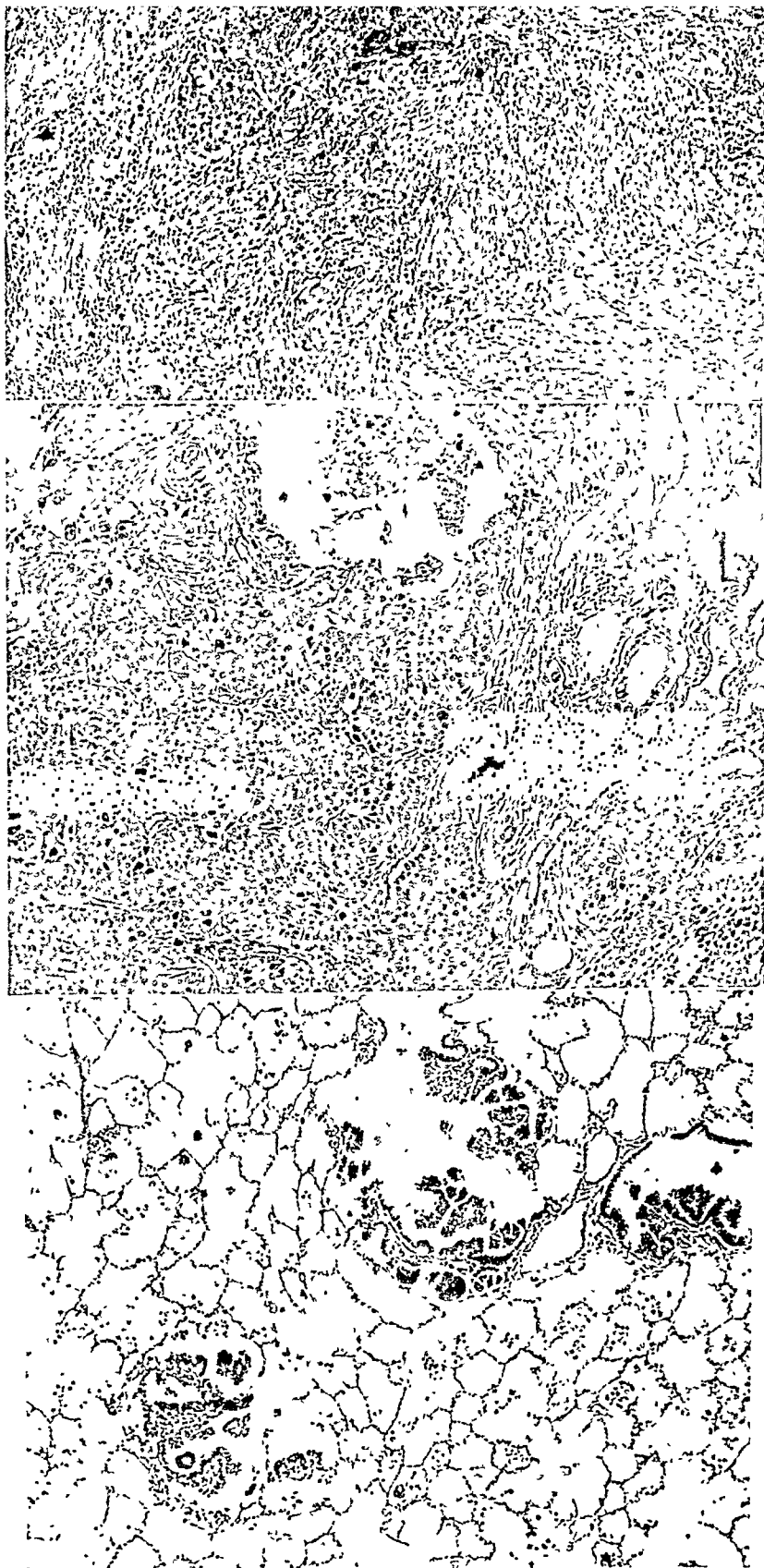
FIG. 8. Chest film taken April 15, 1943, six weeks following lobectomy. The lung fields are free of demonstrable disease. The high diaphragm on the right is secondary to lobectomy.

FIG. 5. (Top) Nonciliated columnar epithelial cells focally line various groups of alveoli. Some are hyperplastic and thrown into papillary folds. The alveolar stroma is preserved and shows no evidence of having been invaded by epithelial cells. ( $\times 67$ )

FIG. 6. (Centre) Section taken from one of the more dense, cellular areas showing marked proliferation of columnar epithelial cells resulting in the formation of intraalveolar papillary and cystadenomatous masses. Again, the alveolar stromal architecture is preserved. ( $\times 67$ ).

FIG. 7. (Bottom) Capillaries in the alveolar septal walls are lined by endothelial cells and separated from intraalveolar air by columnar epithelial cells. These are quite uniform and show no mitotic figures. ( $\times 534$ )





FIGS. 9-11

tan. No definite tumors were readily evident, although close inspection revealed occasional small grayish-white nodules measuring up to 0.1 cm. in width. An old hemorrhagic infarct, 5.0 cm. in width and 2.5 cm. in depth, was present in the periphery of the lower lobe. A slender grayish-tan thrombus plugged a branch of the pulmonary artery which supplied the infarcted area. The peribronchial lymph nodes were small, anthracotic and revealed neither scar nor tumor. The bronchi were patent as far as they could be dissected and were lined by an intact mucosa free of tumor nodules.

Fibrous adhesions covered the pleura of the right lung which was small and had an estimated weight of 200 g. Its lower lobe had been removed surgically. The pleura over the middle lobe was puckered, overlying an old grayish-tan infarct of triangular shape which measured 1.5 cm. in width and 1.1 cm. in depth. The remaining pleura was dotted by a few widely scattered milky-gray patches of thickening which measured up to 0.7 cm. in width. The cut-section of the parenchyma was found to contain a number of tiny grayish-tan nodules which measured up to 0.2 cm. These were most abundant near the base of the upper lobe. Throughout the upper lobe there existed a definite thickening and induration of the septa. A firm, dark grayish thrombus occluded the pulmonary artery. The peribronchial lymph nodes were small, anthracotic and showed no gross tumor.

The heart was normal in size and weighed 300 g. There existed a marked dilatation of the right ventricle with the formation of a prominent pulmonary conus. A grayish thrombus was firmly attached to the endocardium in the tip of the right auricular appendage. Both leaflets of the mitral valve showed a slight nodular thickening proximal to the line of closure. The *chordae tendineae* were very slightly thickened. Arising from the edge of one aortic cusp was a rough verrucous vegetation measuring 0.5 x 0.3 cm.

The uterus was small and freely movable. Both cervical lips were absent. There was extensive greenish-black necrosis (postradiation) of the endocervical and lower endometrical mucosa. Infiltrating the myometrium for a short distance from the necrotic surface was a firm, dirty-white tumor. The vaginal mucosa was pale and smooth except in the region of the fornices where its discoloration was similar to that of the endocervical canal.

Tumor nodules, metastatic from the uterine tumor, were found in various organs and tissues. Contained within the omentum near its tips was a sessile nodule 1.1 cm. in width. Five widely separated noncircumscribed white nodules occurred in the mesentery midway between its root and the mesenteric attachment of the intestines. These nodules varied from 0.5 to 1.4 cm. in size. Smaller, sessile nodules, frequently confluent, varying from 0.3 to 0.8 cm., were present beneath the peritoneal surface of the right leaf of the diaphragm. None was present on the pleural aspect. Present in the midportion of the right ilium was an oval white tumor nodule which measured 1.5 cm. in width.

The left adrenal appeared slightly enlarged, showed considerable depletion of cortical lipid and upon cut-section contained a sharply circumscribed, cream-colored cortical

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FIG. 9. (Top) Adeno-acanthoma cervix uteri. Chiefly comprising the tumor are sheets and strands of spindle to polygonal epithelial tumor cells of the squamous variety. In the upper part of the illustration an acinar arrangement is present. The squamous glandular components are extremely variable in different sections. The squamous component is emphasized in the above photomicrograph. ( $\times 67$ )

FIG. 10. (Centre) Adeno-acanthoma, metastatic to omentum. The architecture and composition of the metastasis is very similar to the neoplasm of the uterine cervix. It is totally dissimilar from the papillary adenomatous lesions in the lungs. ( $\times 67$ )

FIG. 11. (Bottom) Epizootic pulmonary adenomatosis (Icelandic). Focal intra-alveolar papillary hyperplasia of columnar epithelial cells. ( $\times 67$ )

nodule 1.0 cm. in diameter. Each kidney weighed 90 g. Aside from several small infarcts in the left kidney each contained several small, pale, firm nodules which were slightly elevated and varied in width from 0.15 to 0.4 cm. The liver weighed 1,250 g. Several firm, round tumors occurred beneath the capsule and were scattered throughout the parenchyma. The subcapsular nodules showed beginning umbilication. In addition to the tumors, there were a number of subcapsular and parenchymal cysts with smooth linings and thin serous fluid content which measured up to  $3.5 \times 2 \times 1.5$  cm. The pancreas contained one firm, poorly circumscribed, cream-colored tumor which measured  $1.8 \times 1.5 \times 1.0$  cm. It was situated in the body along the superior aspect of the pancreas. The thyroid gland was small, firm and weighed 14 g. (after formalin fixation). It contained several scattered patches of dense, grayish-white "scar" tissue. Otherwise it appeared normal except for slight colloid nodulation of each lobe.

Histological studies of the autopsy specimens revealed two distinct types of tumor as well as bizarre metaplastic changes in some of the organs. Uniformly, the metastases presented a structure compatible with origin from the uterine lesion rather than from the alveolar lesions of the lungs.

Histological sections of the lungs presented concurrent neoplastic lesions. Foci showing replacement of alveolar septal cells by columnar epithelial cells thrown into papillary folds were widely scattered and occurred in moderate numbers. These foci and their cells appeared identical to the hyperplastic cells and arrangement seen in the lobectomy specimen. Such collections, interpreted as pulmonary adenomatosis were quite distinct in appearance from the other type of tumor which was present. This latter occurred chiefly as solid masses of large spindle-shaped epithelial tumor cells (squamous?) which showed all variations in morphology to cells which were smaller, polygonal, and arranged in irregular acinar patterns. In contrast to the papillary adenomatous foci, mitotic figures occurred frequently. The tumor was invasive, infiltrating the supporting septa, lymph vessels and perivascular sheaths of medium sized arteries. In the foci of alveolar papillary adenomatosis, the cells were remarkably uniform in size, shape, staining characteristics and paucity of mitotic figures. This was in contrast to the other neoplastic areas where there was marked pleomorphism of the tumor cells and the occurrence of numerous mitotic figures. Near one focus of alveolar papillary adenomatous hyperplasia there occurred a number of short stubby, slightly globular, papillary projections which were covered by small, polygonal epithelial cells (X-ray effects?). The mucous membrane of the bronchus consisted of pseudostratified columnar epithelium which showed no metaplastic or proliferative changes. A peribronchial lymph node showed the lymphoid architecture to be subtotally replaced by tumor which occurred in closely packed, narrow strands and columns. The tumor cells in the lymph node varied from cuboidal to low columnar.

Sections of the primary uterine tumor showed extensive replacement of the endocervical mucosa by superficially necrotic tumor. The tumor was pleomorphic: in some areas it was glandular and elsewhere epidermoid. These components in places occurred individually, and in some places in intimate relationship to one another. Mitotic figures were not numerous. Throughout both components most of the nuclei stained poorly, were vacuolated and appeared to be degenerating. The histological structure of the adeno-acanthoma is shown in figure 9.

A tumor nodule in the omentum is quite similar histologically to metastatic nodules occurring elsewhere, such as in the bone (ilium), liver, subserosa of small intestine, adrenal, etc. The omental nodule, for example, was composed of irregular, solid strands of epithelial tumor cells amongst which there occurred an admixture of irregular atypical glands of

varying size (figure 10). The solid strands contained polygonal and spindle-shaped epithelial cells, some of which were in whorls showing a slight attempt at the formation of keratohyalin. A slightly basophilic homogeneous substance was contained in a number of the glands. Cuboidal to columnar epithelial tumor cells lined the latter.

Unusual metaplastic-like changes were noted histologically in the kidney, pancreas and thyroid. A tumor nodule in the cortex of the kidney was composed of slender, irregular, solid cords of large cuboidal to polygonal epithelial tumor cells. Mitotic figures were numerous. There existed an abundant fibrous stroma. In places, cytological features suggested an alteration of preëxistent renal tubules rather than the presence of extrinsically invading tumor. Again, in a section of pancreas "a poorly circumscribed tumor nodule is pleomorphic possessing both glandular and squamous components. In places, the gland-like structures are small, and even though atypical, show transitional changes where they are distinguished with difficulty from the normal preëxisting acinar parenchyma of the pancreas. Another notable feature is the marked hyperplasia of the islets of Langerhans, —several not only being large but surrounded by small satellite clusters of islet cells." Aside from certain focal proliferative areas of obscure nature, the parenchyma of the thyroid gland appeared quite normal. In such areas small acini were densely grouped, almost uniformly devoid of colloid, and were lined by hyperchromatic cuboidal epithelial cells. A few showed mitotic figures. These areas appeared to be definitely thyroid in origin rather than metastatic. A picture of basophilism was presented by the hypophysis which showed a massive infiltration of the *pars nervosa* by basophilic cells.

*Anatomical diagnosis:* (1) Adenoma, lung, multiple, alveolar (pulmonary adenomatosis); (2) carcinoma, uterus (adeno-acanthoma, cervix uteri) with metastases to the peritoneum, liver, pancreas, omentum, adrenal, kidneys, bone (right ilium), lung and peribronchial lymph node; (3) metaplasia (?), kidney, pancreas, thyroid; (4) hyperplasia, islets of Langerhans, focal; (5) infiltration, pituitary gland, basophilic, moderate (*pars nervosa*); (6) malformation, congenital, cyst of liver, multiple; (7) thrombosis, pulmonary artery, old, with multiple pulmonary infarcts; (8) endocarditis, acute, bacterial, terminal of aortic valve with multiple infarcts of left kidney; (9) aortitis, chronic, mild (nonspecific).

*Discussion of autopsy findings:* This is a case of multiple neoplasms occurring in a patient who originally presented herself with an abscess for which a lobectomy was performed. Histologically, the removed lobe showed a "pulmonary adenomatosis" which is remarkably similar to the lesions of *Jaagsiekte* (epizootic pulmonary adenomatosis). At autopsy, there was found, in addition to residual pulmonary adenomatosis, an adeno-acanthoma of the uterine cervix which had given rise to numerous metastases. The two neoplastic processes consistently appeared to be quite distinct. Bizarre proliferative lesions in the kidney, pancreas and thyroid suggest somewhat the possibility of a neoplastic transformation of the respective parenchymal cells. A metastatic origin of the nodules in these three organs, however, cannot be excluded with certainty. The lesions directly responsible for the patient's death were thrombotic and endocarditic. The former were associated with occlusion of the right pulmonary artery. A recent vegetative endocarditis of the aortic valve was the origin of small infarcts in the left kidney, and upon being cultured produced a heavy growth of *Staphylococci aureus* (coagulase positive).

#### DISCUSSION

Pulmonary adenomatosis presents a number of interesting problems. One pertains to the histogenesis of the cells. Where do they come from? Do they connote the continued persistence of epithelial cells in the lining of alveolar spaces? What bearing does this disease have upon the controversy amongst

anatomists as to whether or not epithelial cells persist in the lining of alveolar spaces? Second, there is a striking similarity between the morphological features of human cases and those occurring in sheep. The third main problem has to do with etiology. Evidence to date indicates that the ovine disease is communicable. A certain amount of indirect evidence is available which indicates that the disease, at least in sheep, may be due to a virus. Does this disease play any rôle in the pathogenesis of alveolar cell carcinoma of the lung? The wide distribution of the lesions in our case, its obvious chronicity and rarity of mitotic figures are remarkable. How often has this disease been mistaken for carcinoma of the lung, either primary or secondary? Not only in sheep but in the few human cases reported to date dyspnea has been an outstanding symptom.

(1) *Persistence of alveolar epithelial cells in postnatal lungs:* The question as to whether or not epithelial cells participate in the lining of alveoli has not been settled and is still the subject of controversial opinion. Bell (8) in reporting a recent case of diffuse alveolar epithelial hyperplasia in man states, "it seems established that in the postnatal lung the alveolar walls are largely bare of epithelium but that occasional epithelial cells may be found. This disappearance of the alveolar lining is presumably a functional alteration favoring a more rapid interchange of gases between the blood and the alveolar air, and it may be compared to the disappearance of the endothelial lining of the glomerular capillaries which promotes filtration through their walls." Geever, Neubuerger and Davis (11) also in a recent article recognize the existence of epithelial-like septal cells in the alveolar lining, but in discussing tumors arising from these cells prefer the term "alveolar cell tumor," leaving open the question as to the nature of the alveolar cells. These authors present an able review pertaining to the pulmonary alveolar lining under various pathological conditions in man and in animals. They were unable to find evidence of continuous "alveolar epithelium" in normal adult lungs, finding only occasional scattered septal cells. It is quite widely recognized that epithelial-like lining cells are readily found in a wide variety of pathological conditions. Foremost amongst these conditions are chronic passive congestion, lipoid pneumonia, chronic interstitial pneumonia, chronic tuberculosis and post-irradiation effects. Proliferation of alveolar epithelium-like cells has also been induced experimentally by the use of tar and tar derivatives. Grady and Stewart (12) produced multiple tumors of alveolar origin by a subcutaneous injection of either 1:2:5:6-dibenzanthracene or methylcholanthrene into strain-A mice. These tumors in mice ultimately became malignant, but in their initial stages presented a histological appearance similar to that seen in *Jaagsiekte*. The whole question of the nature of the lining alveoli from the histologist's point of view has been recently reopened by Ham and Baldwin (13). Fried (14) thinks that capillaries in the alveolar walls are naked and unprotected by a film of epithelium. Suffice it to say for the purpose of this paper, the present accumulated evidence favors the persistence of occasional scattered epithelial cells in the lining of the alveolar wall. These persistent

cells are the ones which, under certain conditions, may be stimulated to hyperplasia and even neoplasia. In our case, columnar epithelial cells appear to arise *de novo* from the alveolar walls (figures 5, 6 and 7).

(2) *Morphological similarity between the human and ovine (Jaagsiekte) lesions:* Human pulmonary adenomatosis differs considerably from any other known pulmonary lesion occurring in man. Histologically, the hyperplastic alveolar lesions in the two species appear identical. In sheep, however, hyperplastic papillary masses may also arise from the lining of the small bronchioles. Both diseases are characterized by multicentricity of lesions, the occurrence of tall, nonciliated, columnar epithelial-like cells, paucity of mitotic figures and absence of stromal invasion. Two of the human cases reported in the literature were associated with metastases to the peribronchial lymph nodes. These are the cases of Obendorfer (3) and Briese (7). There is only one instance in the literature where metastasis has been observed in *Jaagsiekte*. Dungal (10) cites a report by Aynard (15) who found metastases in one case of *Jaagsiekte*. In both diseases, there are foci where the alveolar walls become lined by a tall columnar epithelium which soon becomes papillary and eventually leads to the appearance of papillary cystadenoma with the formation of definite alveolar structures. Later, the supporting stroma may become thickened, slightly edematous and infiltrated by a few scattered phagocytic cells. It seems that the stromal changes as well as the bronchiolar lesions in *Jaagsiekte* are essentially secondary in importance to the hyperplasia of columnar epithelium in the lining of the alveoli. In view of the striking similarity between the human and ovine diseases, and the fact that the ovine variety is communicable and productive of epizootical spread in all countries in which it has appeared, a short review of *Jaagsiekte* seems warranted at this time.

(3) *Jaagsiekte:* Pulmonary adenomatosis in sheep constitutes a very interesting chapter in veterinary medicine. It is known in different geographical localities by a number of different names. In South Africa, where its existence has been recognized since about 1893 (16) but first scientifically studied by Robertson (17) in 1904, the disease is known as *Jaagsiekte*. Cowdry (16) made a comprehensive study of the disease in the Trasvaal in 1925 and points out that the name *Jaagsiekte* is apt. It is "derived from the Dutch words *jagt*, to drive, and *ziekte*, a sickness, the combination of which is intended to indicate that the initial symptoms become first noticeable when the animals are driven for some distance."

An ovine disease in England known as "verminous pneumonia" was formerly supposed to have been caused by the lung worm, *Muellerius capillaris*. The English veterinary authority, Sir John M'Fadyean, who had in former papers (18a, 18b) felt that the parasitic lung worms were responsible for the disease in England, now feels (18c) that so-called verminous pneumonia is identical with *Jaagsiekte*. He agrees with Dungal, Gisslasson and Taylor (19a, 19b) in excluding lung worms from any possible etiological rôle. These investigators feel that *Jaagsiekte* (South Africa), epizootic adenomatosis (Iceland), verminous

pneumonia (England) and progressive pneumonia of sheep, "lunger disease" (Montana), are very similar, if not identical. In the Montana variety, however, the epithelial proliferation is not so pronounced.

In Iceland the disease is known as epizootic adenomatosis and sometimes as *Deilartunga disease* (after the name of a farm on which the first case is thought to have occurred). In an excellent study (19), initiated in 1936 (at the request of the Icelandic government), Dungal and Gisslasson of the University of Reykjavik, and Taylor from the Ministry of Agriculture of Great Britain, have clearly described epizootic adenomatosis in the lungs of sheep and compared it with *Jaagsiekte*, verminous pneumonia and progressive pneumonia. In the Icelandic material one finds the most clear-cut evidence favoring an "infectious" nature of the disease. Dungal and associates point out that in Iceland (where climatic conditions may vary the course of the disease) the duration after onset of symptoms is extremely variable, ranging from a period of one to two weeks up to one to six months with an average of two to three months. The disease is very insidious in its onset. It runs a chronic course so that weeks may elapse before its presence may be suspected, even by an experienced observer. "Indeed, if the disease has not reached an advanced stage, a flock at rest, containing many affected sheep, may be looked at most carefully, without any sickness being noticed." There is no loss of appetite and but little loss in condition until the latest stage, when the sheep are apt to become very emaciated. A cough, at first dry, is ultimately associated with the development of moist râles on auscultation. "Where the disease has reached an advanced state the breathing causes a characteristic sound which may be heard by anyone standing in the midst of the affected flock, the multiple râles resembling the sound of slowly boiling porridge." Ultimately, the condition becomes productive of much secretion, at first thin and frothy which pours out of the nostrils when the sheep inclines its head towards the ground. Until or unless a terminal secondary infection sets in, the disease characteristically runs an afebrile course. In a detailed study of 13 farms, Dungal and his associates were able to establish a rather uniform incubation period which varied from six to eight months. They demonstrated an hereditary factor. Sheep of the *Gottorp* strain were found to be quite highly susceptible in contrast to those of the *Adalbol* strain. Attempts to demonstrate bacteria, virus or protozoa which might be causative have been uniformly negative. Similarly, attempts to transmit the disease to farm animals of other species and to laboratory animals have also been unsuccessful. In one instance, however, they report that in one of three attempts they succeeded in obtaining successful transmission of the disease by intrapulmonary inoculation. In contrast to these difficulties the transmission can be easily effected by housing sheep together with one or more diseased animals. The serious economic aspect of the disease in Iceland is emphasized by the fact that during the course of about one and a half years it usually causes the loss of about 50 per cent of an affected flock. Again, the histological picture of epizootic adenomatosis is very distinct, consisting of epithelial proliferations forming papillary intraalveolar masses which are noninvasive, singularly preserving the alveolar stromal outlines.

Figure 9 shows the histological appearance of this disease.<sup>4</sup> Variably, there may be a mild exudation of mononuclear cells (phagocytes) into the alveoli.

(4) *Occurrence of similar alveolar hyperplastic lesions in other animals:* Somewhat similar lesions of alveolar septal cells have also been noted in horses and in guinea pigs. Information relative to such a disease in these species is scant. Theiler (20) studied so-called *Jaagsiekte* in horses in South Africa and found that the lesions were predisposed to by the eating of a poisonous plant (*Crotalaria dura*). Since the institution of preventive measures, the disease in horses has been banished from the Union of South Africa. Grumbach (21) found diffuse alveolar epithelization in guinea pigs which he had injected with a diphtheroid bacillus obtained from a lymph node of a patient with Hodgkin's disease. Cowdry (16), who studied these sections, considered the guinea pig lesions similar to those seen in *Jaagsiekte*. Somewhat similar features have been reported by Olafson and Monlux (22) as occurring in toxoplasmic pulmonary infection in a cat. True neoplasms have been reported as occurring spontaneously from the alveolar walls in mice.

In contrast to the intraalveolar hyperplastic lesions just cited, the spontaneous occurrence of tumors from the alveolar walls in mice has been noted by Wells, Slye and Holmes (23).

(5) *Etiology:* Bonne (5), in reporting a case in a Chinese male aged thirty years, was struck with the virus possibility. Having established the diagnosis six months prior to death in our case, we anticipated future studies in regard to a possible virus etiology. Rous (24) pointed out that if the disease is due to a virus there may well be a neutralizing antibody circulating in the blood which during life cannot get at the virus because of its association with living cells, but will, once the cells are dead. Therefore, he suggested that the blood in the lung be flushed out by brief perfusion with salt solution prior to obtaining material for animal inoculations. As noted previously, this was done by cannulating the pulmonary artery, sterile technique being followed as closely as possible during the autopsy. Experiments are now in progress with the material thus obtained, and will be subsequently reported. Rous also suggested that, in view of the successful transmission of human influenza to ferrets, jumping a wide biological gap, it would be worth while to utilize many species, of small animals especially, in trying to transmit the disease. He cautioned us to use great care in protecting ourselves, masks, room ventilation, etc., perhaps glycol sterilization of the atmosphere, if tests are undertaken with monkeys, "for there is no knowing how readily the disease may be transferred." Blood was also obtained several days before the death of the patient for agglutination and complement fixation studies.

In further subsequent correspondence, Rous states, "it seems to me that close behind the demonstration of a virus cause for the disease—which is the immediate problem—there stands the possibility that this virus, if introduced into

<sup>4</sup> This photomicrograph was made from a slide of Icelandic epizootic adenomatosis received through the courtesy of Dr. E. A. Benbrook, Professor of Veterinary Pathology, Iowa State College of Agriculture and Mechanic Arts.



strange hosts, might give rise to adenomas which in course of time would be succeeded by carcinomas. This is what happens with the Shope papilloma virus. Hence it might be highly worth while to inoculate a wide variety of animals. The cell specificity of the neoplastic viruses is peculiar. Often they are capable of attacking cells of the same sort in different species and yet are restricted to those of a single kind in even the species to which they are native. The papilloma virus, for example, is capable of acting upon the epidermis of every kind of rabbit or hare that we have tested, yet it will not 'take' upon mucous membranes even when they have come to resemble the epidermal layer histologically as result of the deprivation of vitamin A. It is for this reason that lung inoculations would offer most promise."

Taft and Nickerson (9) cite an instance where the diagnosis was made by frozen section at the autopsy table, followed by unsuccessful attempts to produce a similar condition in experimental animals by the usual methods. They state further "that the microscopically similar disease in sheep is of an infectious nature undoubtedly true, but the transmission of the disease from sheep to sheep or to any other laboratory animal has been almost universally unsuccessful. However, the disease has been proved to be infectious in nature, as is evident from a study of the epidemic which occurred in Iceland. It seems that a virus is the most tenable cause for the hyperplasia, since no bacterial species has been recovered with any regularity from the affected sheep."

Cowdry (25) has suggested in a personal communication that possibly "the stage is being set for the recognition of another virus disease of the lungs. The evidence in Africa and in Iceland that lesions of this kind in sheep are infectious is impressive." In our material, Cowdry noted several nuclear inclusions but not of the kind most indicative of virus action. Bell (8) states, "the etiology of *Jaagsiekte* is unknown, but its infectious nature and the peculiar proliferation reaction limited to alveolar epithelium suggest a virus."

(6) *Relationship to alveolar cell carcinoma of the lung*: There is a wide-spread opinion that all carcinomata of the lung arise from the bronchus, yet there are a few reported cases with strong evidence of alveolar origin. Smith and Gault (26), Sweany (27), Neuburger (28) have made recent reports of malignant alveolar carcinomata productive of metastases. Thus, it would seem that persistent alveolar epithelial cells may give rise to either benign hyperplasia or to malignant neoplasia, with possible imperceptible transition between the two types of proliferation which may be in response to various specific agents.

#### COMMENT

We have presented a case of diffuse alveolar epithelial hyperplasia in which the diagnosis had been established by lobectomy six months prior to death. The duration of the pulmonary disease is at least two and one half years, the first symptoms being relative to the development of thin-walled "tension" cavities in the right lower lobe. An adeno-acanthoma of the uterine cervix developed independently and late in the course of the pulmonary disease. The adeno-acanthoma had given rise to wide-spread metastases. Metastases in the

lungs and peribronchial lymph nodes possessed a structure distinctly different from the multicentric foci of alveolar epithelial proliferation found in the excised lung tissue and in a few small scattered foci which were found in the other lobes at the time of the autopsy. Of further interest is the finding at autopsy of bizarre metaplastic areas in the thyroid, kidneys and pancreas, where the cytoplasmic and nuclear morphology is so disturbed as to suggest incipient neoplasia. The pulmonary lesions, uterine adeno-acanthoma and the bizarre metaplastic areas in the thyroid, pancreas and kidneys suggest the generalized stimulating action by some unknown agent or agents, gradually breaking down the orderly behavior of proliferative repair in various organs. For the present we must assume that the pulmonary alveolar epithelial hyperplasia is independent of the uterine malignancy. In view of its striking morphological resemblance to *Jaagsiekte* in sheep, a probable virus etiology is considered and discussed. In view of this probability necessary safeguards were taken in the procuring of autopsy material for animal and serological studies, subsequently to be reported. We feel that a search should be made for similar cases, and that similar studies should be undertaken when possible.

#### SUMMARY

1. A case of histologically benign pulmonary epithelial adenomatosis occurring chiefly in the right lower lobe of a telephone operator, fifty-seven years of age, has been reported.

2. This is the first case in which the disease had been diagnosed prior to death, and found apparently restricted at that time to one lobe.

3. Prior to lobectomy the patient had presented pulmonary symptoms for two years.

4. Dyspnea with an initial dry cough gradually becoming productive constituted a rather prominent feature of the disease.

5. The development of thin-walled tension cavities in the right lower lobe focused clinical attention upon them rather than the other pulmonary lesions. When one of the cavities was opened surgically, sulfanilamide powder was instilled into the wound and the wound then tightly closed.

6. Grossly, the lesions in the lobectomy specimen resembled those of a non-caseating disseminated miliary tuberculosis.

7. Histologically, the most prominent feature is the multicentricity of hyperplastic columnar epithelial cells lining the alveolar walls, showing all degrees of proliferation from simple lining to papillary and cystadenomatous arrangements. In all sections there is a striking preservation of alveolar stroma devoid of epithelial invasion. Only hyperplastic alveolar changes are found, none being present in the bronchi.

8. Clinically, the pulmonary adenomatosis was confined to the right lower lobe for over a year. Foci, however, were found in the other lobes upon post-mortem examination.

9. An adeno-acanthoma of the uterine cervix was discovered three months prior to the patient's death, approximately fourteen months after the patient

was first seen. It had resulted in numerous distant metastases most of which were below the diaphragm. The metastases showed both squamous and glandular components, similar to the primary tumor but distinctly different in morphology from the alveolar adenomatous lesions in the lungs.

10. Bizarre metaplastic changes occurred in the thyroid, pancreas and kidneys, all of which were suggestive of incipient neoplasia.

11. Attention has been focused on the striking morphological similarity between human pulmonary adenomatosis and that which occurs in sheep (*Jaagsiekte*, epizootic adenomatosis, verminous pneumonia, and progressive pneumonia of Montana).

12. The infectious nature of *Jaagsiekte* is discussed and the possible virus origin for the two diseases considered.

#### SUMARIO

1. Comuníquese un caso de adenomatosis epitelial pulmonar histológicamente benigno, que afectó principalmente el lóbulo inferior derecho de una telefonista de 57 años de edad.

2. Este es el primer caso en que se haya diagnosticado la enfermedad antes de la muerte y en que estuviera aparentemente limitada entonces a un lóbulo.

3. Antes de la lobectomía la enferma había acusado síntomas pulmonares por espacio de dos años.

4. La disnea, asociada a una tos seca inicial, que gradualmente se volvió húmeda, constituyó una característica algo pronunciada de la enfermedad.

5. La aparición de cavernas bajo tensión de paredes delgadas en el lóbulo inferior derecho, hizo concentrar la atención clínica en ellas más bien que en las otras lesiones pulmonares. Al incindir las quirúrgicamente se instiló sulfanilamida en polvo en la herida y se cerraron herméticamente.

6. Macroscópicamente las lesiones del ejemplar lobectomizado se parecían a las de una granulía sin caseación.

7. Histológicamente la característica principal consistía en la multicentricidad de células hiperplásicas del epitelio cilíndrico, que recubrían las paredes alveolares y revelaban todos los grados de proliferación, desde mero recubrimiento a disposición papilar y cistadenomatosa. En todos los cortes había una notable conservación del estroma alveolar sin invasión epitelial. Sólo se observaron alteraciones hiperplásicas en los alvéolos, sin ninguna en los bronquios.

8. Clínicamente la adenomatosis estuvo limitada al lóbulo inferior derecho por más de un año, pero en la autopsia se descubrieron focos en los otros lóbulos.

9. Tres meses antes de la muerte de la enferma, o sea unos 14 después de observarla por primera vez, se descubrió un adenoacantoma del cuello uterino que había producido numerosas metástasis remotas, la mayor parte de ellas debajo del diafragma. Las metástasis revelaron componentes tanto escamosos como glandulares semejantes al tumor primario, pero decididamente distintos morfológicamente de las lesiones adenomatosas de los alvéolos pulmonares.

10. En el tiroides, páncreas y riñones había caprichosas alteraciones metaplásicas que indicaban neoplasia incipiente.

11. Se llama la atención sobre la notable semejanza morfológica entre la adenomatosis pulmonar en el hombre y la que se observa en las ovejas (*jaagsiekte*, adenomatosis epizootica, neumonía verminosa y neumonía evolutiva de Montana).

12. Discútese la naturaleza infecciosa de la *jaagsiekte* y el posible origen viral de ambas dolencias.

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# CONGENITAL TUBERCULOSIS

## Its Clinical Importance

ERNST LOEWENSTEIN<sup>1</sup>

All manuals of obstetrics agree that congenital infection with tubercle bacilli means death by miliary tuberculosis within six months. This opinion is founded on the autopsies of about 200 babies; but these reports cannot settle the question of whether there are survivors. This question can only be answered in two ways: (1) by autopsies of babies in whom we find sure signs of a healed focus in the *porta hepatis*, and (2) by examining the umbilical cord for tubercle bacilli and pursuing the fate of babies in whose cord blood tubercle bacilli are found.

### AUTOPSIES

I found only 2 autopsy reports which speak for the possibility of a healed congenital infection. Zarfl reports a case of congenital tuberculosis in which the foci in the liver were in a healing phase, and he concludes: "One could easily imagine that a less severe infection occurring at a later time could terminate in complete healing without the development of miliary tuberculosis." Such a single finding in a single case must change our opinion about the fatality of such cases. Chiari described the other case: a child, two and one-half years old, died of tuberculous meningitis. The autopsy revealed a large primary focus in the liver completely healed, and a probable primary focus in one lung; a sure case of intrauterine infection. The meningitis was accidental; anyway, the child lived thirty months and would have lived longer without the accident of meningitis. Chiari draws the conclusion that "such a case will compel us to correct our conception concerning the absolutely hopeless prognosis of congenital tuberculosis." Chiari induced the mother of this child to have a careful clinical check-up. There were no signs or symptoms of tuberculosis. The X-ray examination showed only fibrosis in both apices with a calcified focus in the right apex. Otto Sachsel, Pediatric Clinician at Prag, reported a case of miliary tuberculosis in a four-weeks-old baby, whose mother was carefully examined by all clinical methods. No symptom of tuberculosis could be detected.

This paper may draw the attention of pathologists to report similar observations.

### TUBERCULOSIS IN THE UMBILICAL CORD

There are only a few papers on this subject, and all the babies reported were born dead or died after a short time. In 1931, Reitter and I published 3 cases in which I cultured tubercle bacilli from the blood of the umbilical vein. The first child was born by a mother who had rheumatic fever and an incipient endocarditis. The blood of the mother was examined twelve times, and three times tubercle bacilli were isolated. One of these three strains was used for animal

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infection; it killed the guinea pig in two months with severe tuberculous lesions. The guinea pig infected with the blood died after five months with generalized tuberculosis. At the time of the delivery, the blood from the cubital vein of the mother and from the umbilical cord was positive in animal experiment and culture.

The mother of the second positive baby had a recrudescant rheumatic endocarditis and polyarthritis. Her blood was positive for tubercle bacilli four times out of seven examinations; also at the time of delivery.

The mother of the third child suffered from rheumatic fever and incipient endocarditis. Her blood was positive for tubercle bacilli six times during seven months, and also at the time of delivery.

All 3 babies appeared normal; they had no symptoms at all for two years and their tuberculin reactions were negative. After about two years, all 3 developed general swellings of the lymph nodes, subfebrile temperature for one to two weeks, pains in the joints, and later enlargement of the liver and spleen (Still's disease?). One child got an otitis media and later jaundice. I isolated tubercle bacilli from the faeces. The swelling of the lymph nodes fluctuated. These symptoms disappeared, and the 3 children were apparently healthy until March, 1938, when I left Vienna. There were no further symptoms during three to six years of observation.

Calmette and Saenz checked these results and reported at the meeting of the Academy of Medicine in Paris, March 21, 1933, that they found virulent tubercle bacilli by culture and animal experiment in the umbilical cord of 5 babies of tuberculous mothers. The babies remained absolutely normal and tuberculin-negative during the time of observation. Meanwhile, I had extended my investigations by organizing a cooperative investigation with the obstetricians of Vienna, and I got blood samples from 56 tuberculous mothers and the respective umbilical cords. Eight cultures from mother and child were positive out of the 56 cases. In one case only the mother's blood was positive and in another case only that from the umbilical cord. I examined the blood from the cubital vein of 210 apparently healthy mothers and the blood from the umbilical cords and, here, both blood samples were positive in only 2 cases. The babies were apparently healthy and tuberculin-negative during one year of observation.

I received the liver of 3 foetus of mothers whose advanced tuberculosis made the interruption of pregnancy unavoidable. Two livers were positive. Professor Josef Novak sent me a five-months-old foetus, which was already macerated (died *in utero*); the culture was positive from every organ, in spite of the macroscopically normal appearance. The culture from the adrenal glands showed the most numerous colonies. There is an analogy with syphilis, in which the spirochetes are also very numerous in the adrenal glands in case of a spontaneous abortion.

There is another analogy with syphilis: Klasten described a baby in whose umbilical cord many spirochetes could be demonstrated by microsection, but, in spite of that, the Wassermann test remained negative for the time of observation (twelve months), in contrast to the mother whose blood was positive all the time.

These findings are in direct opposition to our expectation and should, therefore, be tested on a large scale, because it would throw light on the mechanism of tuberculosis infection.

There are other interesting papers on this subject. Siegel and Singer published an interesting paper in 1935. Fifteen tuberculous mothers, 9 with advanced and 6 with incipient tuberculosis, were examined, and in one case the culture of cubital vein blood of the mother and of the umbilical cord was positive. The authors summarize:

"Fifteen newborn infants of tuberculous mothers were studied for evidence of the transmission of tubercle bacilli by way of the umbilical vein. Cultures of umbilical blood by the Loewenstein method were negative in fourteen cases, and positive in one case. In the case in which the umbilical blood was positive, the placenta had a large tuberculous area. The child was born prematurely in seven months, and he died three hours after birth, with *no demonstrable lesions on postmortem examination*. A culture from the heart blood was *strongly positive* for tubercle bacilli. The mother died of tuberculosis eighteen hours after delivery."

The number of these cases is too small for far-reaching conclusions, but it does show the value of the culture method. I recommend the application of both methods, culture and animal experiment, and for each method the haemoglobin-free sediment of 10 cc. citrated blood should be used.

Mönckeberg, Onetto and Vergara injected blood of the umbilical cord of a tuberculous mother into three guinea pigs, all of which died of tuberculosis, but the child showed no symptoms of tuberculosis and was found healthy and tuberculin-negative after eight months.

Professor Luksch, director of the Pathological Institute of the University of Prag, wrote me that he found, by animal experiment, in 9 out of 27 tuberculous mothers, tubercle bacilli in the umbilical cord. In spite of this, the babies appeared normal as long as they could be observed. There was no mention of tuberculin reactions.

In summarizing my own experiences, there were 3 children of mothers with rheumatic endocarditis who were observed for three to six years and 10 children who were observed up to one year of age, born by tuberculous mothers. The umbilical cord of these 13 children contained virulent tubercle bacilli, but the babies were tuberculin-negative. I found only one case of intrauterine infection in which tuberculin tests and an autopsy were performed (Lindquist). The child died when seventy-eight days old, with tuberculosis; but it had always been tuberculin-negative.

#### DISCUSSION

The question arises why some of the babies die and others survive? I tried to obtain some information from the autopsy reports; perhaps an analysis of the distribution of the tuberculous foci or the age of the tuberculous lesions could give a hint about the mechanism of uterine infection. First, we may exclude the germinal infection by the way of tubercle bacilli containing sperm. I had 3 cases of testicular tuberculosis with prostatic and vesicular involvement, but the



children of these patients were healthy and tuberculin-negative. One child has grown to be thirty years of age and is healthy. All 3 babies were tuberculin-negative for at least five years. I could not find a single case in the literature in which valid evidence was produced of a germinal infection in human beings.

Therefore, only haematogenous infection is possible. The umbilical cord goes to the *porta hepatis*, there the bacilli could become localized in the fibrous tissue of Glisson's capsule or they could be filtered out by the parenchyma of the liver. The liver surely is a kind of barrier.

But there is the other possibility, that the bacilli are carried into the lungs by way of the *ductus Arantii*, vena cava, right auricle and pulmonary arteries, and perhaps by way of the *ductus Botalli* into the general circulation. The umbilical cord can bring bacilli only from a tuberculous placenta. All experiments with embryo emulsions before the establishment of the placenta were negative. Pehu and Challier collected a series of 51 cases of tuberculous mothers; the animal experiments with embryos up to three months were all negative, just as in Pankow's experiments.

Tuberculosis of the placenta is far more frequent than is generally known. Sitzenfrey found it in 23 per cent; Schmorl and Geipel found tuberculosis in 45 per cent of 20 cases of tuberculous mothers. The results, of course, were more positive in advanced cases; however Schmorl and Geipel emphasize that tuberculosis may be found in the placenta when there is little pulmonary involvement in the mother, such as a small apical lesion. This possibly can be explained by the fact that "tuberculous bacillaemia may occur early in the course of tuberculosis" (Siegel and Singer, p. 637). The placental lesions begin and develop in the intervillous spaces of the placenta where small thrombi, consisting of bacilli, are deposited because the circulation in these lagoons is very slow. How do the bacilli pass from the placenta to the embryo? I tried to learn from the distribution of the foci and their ages what the usual way may be, at least in dead cases. Siegel has made such an analysis of 37 autopsy reports, and he found that the lungs were most frequently involved and that the degree of the pulmonary involvement was usually equal or greater than that of the liver. That means that miliary tuberculosis of the lungs was already developing. Siegel's analysis of the autopsy reports suggests to me that the death of the babies is due to the direct invasion of the lungs. That invasion happens when the tuberculous focus in the placenta is established about four months before the delivery. Then the influx of bacilli lasts for months so that an enormous quantity of bacilli invades the embryo. As a consequence the barrier of the liver breaks down and the lungs are inundated with bacilli. The babies are born dead or die within a short time after delivery of miliary tuberculosis.

The survival of an unknown percentage may be explained by one single invasion during delivery. The contractions of the uterus express the placenta like a sponge and blood and bacillary thrombi of the sinuses are pressed into the umbilical vein. With the ligation of the cord the influx of bacilli, which only lasted for a short time, is stopped so that the liver can arrest the single dissemination.

Nobody will believe that such a tubercle bacilli invasion may leave no traces

in the organism. In the first place we do not know whether the bacilli are killed or only arrested in the liver, encased in calcified tissue. My findings of tubercle bacilli in the faeces of the case with jaundice suggest that only arrest occurred. The bacilli may break out when the natural resistance is lowered by another infection, by undernourishment, overwork, or alteration of the blood vessels, or by vitamin deficiency.

There is the other possibility that such cases are immunized in a way similar to Calmette's BCG vaccination of newborn babies. Bacilli given orally reach the liver and, perhaps, the liver is an important organ for immunity in tuberculosis. I see only one way out of the labyrinth of so many possibilities: that is the careful observation of such babies for the first two decades of their life, with especial regard to rheumatic and other allergic and anergic diseases and the syndrome of dementia praecox.

After this paper was finished, Doctor Pinner drew my attention to a report by Mario Waissman ("El Ateneo," Buenos Aires, 1942), who reported 11 cases of congenital tuberculosis out of 737 babies of tuberculous mothers—or 1.46 per cent—the largest material published to date. He also discovered that the umbilical cord puts off a branch to the spleen.

#### SUMMARY

1. Congenital infection occurs from the placenta and, therefore, not earlier than the fourth month of pregnancy. Germinal infection plays no rôle. Infection by aspiration or ingestion of amniotic fluid is rare.

2. Placental tuberculosis is far more frequent than generally known, even in cases with very small lesions in the lungs.

3. Congenital foci, especially in the liver, may heal spontaneously.

4. Blood from the umbilical cord contained tubercle bacilli in 3 babies whose mothers had rheumatic endocarditis; all 3 babies stayed well. Bacilli were found in the blood from the umbilical cord of 9 cases out of 59 tuberculous mothers; one baby died of miliary tuberculosis. Positive umbilical cord blood was found in 2 out of 210 apparently healthy mothers; the 2 babies remained well.

5. Therefore, the prognosis of congenital tuberculosis is not absolutely hopeless, especially when the blood invasion occurs only during delivery.

6. The autopsy of congenitally infected babies may show no gross lesions, but sections and especially cultures from the heart blood prove the presence of tubercle bacilli.

7. The tuberculin reaction of such babies remains negative for a long time, even in cases in which tuberculosis is proved at autopsy.

8. Examinations of the blood of the umbilical cord should be started on a large scale, especially of mothers with tuberculosis and rheumatic endocarditis.

9. The fate of congenitally infected babies should be observed for two decades.

#### SUMARIO

1. La infección congénita procede de la placenta y por lo tanto no es anterior al cuarto mes del embarazo. La infección germinal no desempeña papel alguno y la debida a la aspiración o ingestión de líquido amniótico es rara.

2. La tuberculosis placentaria es mucho más frecuente de lo que se conoce generalmente aún en los casos en que son pequeñas las lesiones en los pulmones.

3. Los focos congénitos, sobre todo en el hígado, pueden curar espontáneamente.

4. En tres lactantes cuyas madres tenían endocarditis reumática, la sangre del cordón umbilical contenía bacilos tuberculosos; las tres criaturas permanecieron bien. También se encontraron bacilos en la sangre del cordón umbilical de 9 de 59 madres tuberculosas; un lactante murió de granulía. La sangre del cordón umbilical resultó positiva en 2 de 210 madres aparentemente sanas; las dos criaturas continuaron bien.

5. Dedúcese de lo anterior que el pronóstico de la tuberculosis congénita no es absolutamente desesperado, máxime cuando la invasión sanguínea sólo tiene lugar durante el parto.

6. La autopsia de los lactantes infectados congénitamente tal vez no revele lesiones macroscópicas, pero los cortes y sobre todo, los cultivos de la sangre cardíaca muestran bacilos tuberculosos.

7. La reacción de esas criaturas a la tuberculina permanece negativa por mucho tiempo aún en los casos en que se comprueba la presencia de tuberculosis en la autopsia.

8. Deben iniciarse en gran escala exámenes de la sangre del cordón umbilical, sobre todo en las madres que padecen de tuberculosis o endocarditis reumática.

9. La evolución de las criaturas congénitamente infectadas debe ser observada por espacio de dos decenios.

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# FREQUENCY OF TUBERCULOUS LESIONS AT AUTOPSY

## Some Epidemiological Inferences

### (Second Report)

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The authors' first survey (1), commenting upon the frequency of tuberculous lesions in 165 routine autopsies performed at the Washington County Hospital, Hagerstown, Maryland, was published in August, 1941. It was realized at that time that the comparatively small number of postmortem examinations would necessitate an enlargement of the statistical data and a possible revision of the epidemiological inferences drawn from them. The present report, therefore, is intended to bring the figures up to date and to compare the new series (from September 1, 1940 to April 30, 1944) with the former one. In combining the old and the new survey an opportunity is given to reexamine statistically the original epidemiological problems with the help of a considerably larger material.

As to contributions in the available medical literature pertaining to the same question, one only, published in the meantime, covers a comparable field. Carnes in his thesis *The Present Incidence of Tuberculous Infection* (2) has utilized as representative sample the autopsies performed in two large hospitals in the City of Baltimore during the period 1938 to 1940. He comes to the conclusion that in Baltimore "about 70% of individuals have acquired a tuberculous infection by the age of 20 years and that universal infection is approximated only in the age group above 50 years. Taking into consideration the age distribution of the adult population, the data indicate that about 90 per cent of the adults in this city have been infected." Anticipating the author's conclusions at this juncture it will be necessary later on to compare them with the combined Hagerstown series. However, even here it seems necessary to emphasize that the material collected by Landé and Wolff comes from a homogeneous, predominantly white, native-born population which has not been selected as to social and economic factors as was, unavoidably, the case in Baltimore. Thus, differences in the frequency of tuberculous lesions may be due less to differences in investigative methods employed (X-ray pictures of lungs and hilar structures removed at autopsy in the Baltimore series; careful gross examination only in Hagerstown) than to sociological differences between underprivileged population groups in a large town and the average population of a semirural district.

It may further be stated that the percentage of Negroes in the Baltimore survey is much higher, 229 among a total of 536 autopsies, or 42.7 per cent, than in the Hagerstown material, where the number of colored (5 among 165 autopsies) was negligible. In this connection, another point is worth mentioning which has been observed by the author himself. It is striking that the percentage of tuberculous lesions in the Negroes is in several age groups appreciably smaller than in

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the whites. The percentages, of course, are not very significant in the single (mostly five years) age groups owing to the small numbers. However, taking the total series of autopsies one arrives at a percentage of 75.6 positive findings among the whites (232 out of 307) and only 64.2 per cent positives among the Negroes (147 out of 229). The difference of  $11.4 \pm 4.01$  is almost significant in a strict statistical sense, being 2.8 times its standard error. One would rather expect the Negroes to show a higher incidence of positive lesions than the whites in view of the fact that tuberculosis mortality among the non-white races is at least three times as high as among the white race, in the United States as a whole as well as in Maryland.

#### PRESENT RESULTS

Again, as in the first survey, the autopsies have been performed by the same pathologist (K. E. L.) according to the criteria originally laid down by Naegeli (3), and described in the 1941 publication. The material is fundamentally identical: postmortem examinations undertaken in a general, nonprofit hospital, the only one in the county, on people who have been born in or have at least lived the greater part of their lives in Washington County or the City of Hagerstown. Their economic status represents every social level. The autopsy permits have been secured with the help of the staff members of the hospital in a frequency varying between 30 and 40 per cent of the patients dying at the hospital during the period under scrutiny. Since patients with open tuberculosis are not admitted to the institution, the 5 cases encountered are accidental findings not known before death. Sixty-seven outside autopsies which are included in the total material of 275 have been performed either for the deputy medical examiner of the county or at special request of physicians and families of the deceased persons (insurance and related cases). They likewise constitute a group recruited from the same population, only with the difference that most of them have been victims of sudden, unexpected death—natural, accidental or otherwise. Open, active tuberculosis did not occur among this latter group. Among 19 colored persons, not to be separated as a special subdivision on account of the small number, fatal miliary tuberculosis has been encountered once.

Again, as in the first survey, the age groups are arranged below the age of one, from one to nine, and then in groups of ten years. Tables 1 and 1A are self-explanatory, showing the age distribution of all autopsies; they are arranged in such a way that first the new material, 275 autopsies (from September 1, 1940 to April 30, 1944), is presented and then, in identical manner, the whole material (from September 1, 1938 to April 30, 1944) comprising 440 autopsies.

In tables 2 and 2A the new and then the combined material has been arranged, as in the former publication, for persons ten years and over, showing the incidence of positive and negative findings by sex. Counting the cases classified as questionable together with the negative cases, out of 228 persons (both sexes together) 132, or 57.9 per cent, have evidence of tuberculosis and 96, or 42.1 per cent, have been found free. For the combined survey the corresponding figures are: out of

361 autopsies 195, or 54 per cent, are positive; 166, or 46 per cent, are free of tuberculous manifestations.

Tables 2 and 2A contain some additional details as to several subdivisions of tuberculous findings. In tables 3 and 3A these autoptic results are subdivided

TABLE 1

*Age distribution of 275 autopsies, Hagerstown, Maryland, 1940-1944*

AGE IN YEARS	AUTOPSIES	
	Number	Per cent
Under 1	34	12.4
1-9	13	4.7
10-19	8	2.9
20-29	16	5.8
30-39	31	11.3
40-49	49	17.8
50-59	44	16.0
60-69	31	11.3
70-79	36	13.1
80 and over	13	4.7
All ages.....	275	100.0

TABLE 1A

*Age distribution of 440 autopsies, Hagerstown, Maryland, 1938-1944*

AGE IN YEARS	AUTOPSIES	
	Number	Per cent
Under 1	55	12.5
1-9	24	5.5
10-19	13	2.9
20-29	22	5.0
30-39	47	10.7
40-49	67	15.2
50-59	74	16.8
60-69	59	13.4
70-79	54	12.3
80 and over	25	5.7
All ages.....	440	100.0

by age decades. If we take, in compliance with our first report, only the ages between twenty and ninety years to approach the age delimitation of Naegeli (3) and Opie (4) for adults, one finds 130 positive cases among 220 autopsies, or 59.1 per cent in the new material. The corresponding figures of the combined study are 192 positives among 348 autopsies, or 55.2 per cent. Leaving out the active tuberculous cases among the adults twenty years and above, the percentages

decrease to 58.1 and 54.0, respectively. These percentages then represent the incidence of tuberculous lesions among those adult persons who have died of other diseases than tuberculosis, or an "index of frequency of infection in the general population." This index would rise somewhat if the questionable cases were added to the positive ones.

The upward trend in tuberculosis frequency with increasing age, commented upon in our first communication and illustrated in tables 3 and 3A, is equally evident in our new series. Whereas the negative cases still prevail over the positive ones in the brackets between thirty and thirty-nine years, a reversal of

TABLE 2

*Tuberculous lesions in 228 autopsies of persons ten years and over, by sex—1940-1944*

TOTAL AUTOPSIES	MALES 134		Females 94		Both Sexes 228	
	Number	Per cent	Number	Per cent	Number	Per cent
Old healed lesions. . . .	84	64.9	43	47.9	127	57.9
Active tuberculosis:						
Fatal. . . . .	1		1		2	
Concomitant. . . . .	2		1		3	
Questionable cases. . . . .	6	35.1	2	52.1	8	42.1
Negative cases. . . . .	41		47		88	

TABLE 2A

*Tuberculous lesions in 361 autopsies of persons ten years and over, by sex—1938-1944*

TOTAL AUTOPSIES	MALES 224		Females 137		Both Sexes 361	
	Number	Per cent	Number	Per cent	Number	Per cent
Old healed lesions. . . . .	121	56.7	65	49.6	186	54.0
Active tuberculosis:						
Fatal. . . . .	2		1		3	
Concomitant. . . . .	4		2		6	
Questionable cases. . . . .	9	43.3	4	50.4	13	46.0
Negative cases. . . . .	88		65		153	

the figures, with prevalence of positive findings, is noted from the age group forty to forty-nine on. The highest proportion of positive results is encountered in the age group eighty years and over (11 positive cases among 13 autopsies in the new survey, 19 among 25 in the combined material). On account of the small numbers in the single age decades we did not show percentages. Nevertheless, the upward trend with age cannot be doubted in this survey nor in most other reports of a similar kind.

The problem of eventual pathogenicity of calcified lesions on animal inoculation has not been broached, as not being within the scope of this review. However,

the reader is referred to newer autopsy findings and animal experiments in this special field as published by Sweany (5) in his recent publication. Active tuberculous lesions, fatal twice and concomitant three times, again have been observed in this new autopsy series. Mention is made of these instances here only in order to underline the "case finding value" of postmortem examinations for public health purposes.

TABLE 3

*Tuberculosis findings in 275 autopsies by single age groups, 1940-1944*

	AGE GROUPS IN YEARS									All ages
	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	
Total autopsies.....	47	8	16	31	49	44	31	36	13	275
Old healed tuberculosis.....	1	2	5	13	24	25	21	26	11	128
Active tuberculosis.....	1	—	—	—	2	2	1	—	—	6
Questionable cases.....	—	—	—	—	1	2	1	3	1	8
Negative cases.....	45	6	11	18	22	15	8	7	1	133

TABLE 3A

*Tuberculosis findings in 440 autopsies by single age groups, 1938-1944*

	AGE GROUPS IN YEARS									All ages
	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	
Total autopsies.....	79	13	22	47	67	74	59	54	25	440
Old healed tuberculosis.....	1	3	5	20	33	35	35	36	19	187
Active tuberculosis.....	3	—	—	1	2	4	1	—	1	12
Questionable cases.....	—	—	—	—	2	3	4	3	1	13
Negative cases.....	75	10	17	26	30	32	19	15	4	228

#### DISCUSSION AND EPIDEMIOLOGICAL CONCLUSIONS

Percentages of the frequency of positive findings at autopsy were not shown by age decades in the preceding tables. However, we might be entitled to compute, as in the former report, percentage frequencies for three main age groups, 0 to nineteen, twenty to forty-nine, fifty years and over (which about correspond to the children, parent and grandparent ages according to population theory). All autopsy figures for the combined material in these broad age groups now approach or surpass 100 cases.

In spite of a somewhat higher frequency of positive findings in the new material (48.7 for all ages against 39.4 per cent in the old material), the percentage in both surveys, and, therefore, also in the combined material of 440 autopsies (45.2 per cent), performed in the six years from 1938 to 1944, stays below 50. These per-



centages include the active cases but exclude the questionable ones. The summaries in tables 4 and 4A further make it clear that in spite of certain differences within the columns the general trend of the positive results is very similar to the results published in 1941.

First of all, it is again obvious that the frequency of tuberculous lesions rises distinctly from childhood to adult ages. The percentage in the years under twenty being only 7.3 in the new survey (as against 8.1 in the 1938-1940 report and 7.6 in the combined material) jumps to 45.8 in the adult ages twenty to forty-nine years (as against 42.5 in the former report and 44.9 in the combined material). All these differences are not significant in a statistical sense. Yet the

TABLE 4

*Total number of autopsies and tuberculous lesions, by three main age groups, in Hagerstown, Maryland, 1940-1944*

AGE IN YEARS	TOTAL AUTOPSIES	TUBERCULOUS FINDINGS	
		Number	Per cent
0-19	55	4	7.3
20-49	96	44	45.8
50 and over	124	86	69.4
All ages.....	275	134	48.7

TABLE 4A

*Total number of autopsies and tuberculous lesions, by three main age groups, in Hagerstown, Maryland, 1938-1944*

AGE IN YEARS	TOTAL AUTOPSIES	TUBERCULOUS FINDINGS	
		Number	Per cent
0-19	92	7	7.6
20-49	136	61	44.9
50 and over	212	131	61.8
All ages.....	440	199	45.2

frequency of positive findings rises still higher in the ages over fifty years. The percentage in the present report amounts to 69.4 (as against 51.1 in the 1938-1940 report and 61.8 in the combined material). These differences in the age group fifty years and over are in all likelihood beyond the limits of mere chance fluctuations. If one computes, for instance, the standard error of the difference for the two independent groups, 1938-1940 and 1940-1944, the result is:

$$\text{Difference } (69.4 - 51.1) = 18.3 \pm 6.75.$$

Exactly the same statistical significance is obtained if the errors are computed for the general group of the combined material and one of the subsamples. This, of course, must be necessarily so if the changed formula for those not independent

samples is applied.<sup>3</sup> The differences are then between the total group and the 1938-1940 survey:

$$\text{Difference } (61.8 - 51.1) = 10.7 \pm 3.96;$$

between the total group and the 1940-1944 survey:

$$\text{Difference } (69.4 - 61.8) = 7.6 \pm 2.81.$$

In all three cases the statistical significance is the same, the various differences being 2.7 times their standard errors.

Thus the increase in positive findings for the age group fifty years and over, from the former to the latter survey, represents a difference beyond the probable limits of chance; and it may be a reasonable explanation that this increase in the higher ages is due to an improvement in technique and experience just as it was reported in Naegeli's successive surveys. Considering, however, the frequency of positive findings in all adult ages together, twenty years and over, one arrives

TABLE 5

*Total number of autopsies and tuberculous lesions, by three main age groups, in Baltimore, 1938-1940 (after Wm. H. Carnes (2))*

AGE IN YEARS	TOTAL AUTOPSIES	TUBERCULOUS FINDINGS	
		Number	Per cent
0-19	146	24	16.4
20-49	213	181	85.0
50 and over	177	174	98.3
All ages.....	536	379	70.7

at a percentage of 59.1 in the new series as compared with 48.4 in the former one, and 55.2 in the combined material. The differences are not statistically significant. The latter percentage may be taken as a minimum figure in the Hagerstown studies. This percentage again is much lower than were Naegeli's original values from Switzerland and Opie's values from this country at the beginning of the century.

In the investigation of Carnes for the city of Baltimore the frequency of positive findings was still almost as high as in the original investigations of Naegeli and Opie. In order to compare the Baltimore results with our own, the figures of Carnes as given in his table 1 for smaller age groups are rearranged according to our table 5 in the following summary:

The Baltimore survey was made in the same calendar years (1938-1940) as our

$$^3 E \text{ diff.} = \sqrt{\frac{pq}{n_1 + n_2} \cdot \frac{n_2}{n_1}}, \text{ where } n_1 \text{ and } n_2 \text{ are the numbers of the subsamples, } n_1 + n_2 =$$

$N$ , or the number of the entire sample. Therefore,  $\sqrt{\frac{pq}{n_1 + n_2}} = \sigma_N$  (see Yule and Kendall (6, p. 362)).

first report. After adjustment to our age delimitations, the frequencies in Baltimore for the age groups 0 to nineteen and twenty to forty-nine years are, with 16.4 and 85.0 per cent, respectively, exactly double those reported for Hagerstown (8.1 and 42.5). In the ages fifty years and above, the frequency of positive findings in Baltimore reaches almost 100 per cent, and for all adult ages together, twenty years and above, it is still 91.0 per cent. In view of the fact that the mortality from tuberculosis in Baltimore and in the state of Maryland during the last three to four decades has as much decreased as in other parts of the country, at least for the white population, the high and almost unchanged frequency of positive tuberculous lesions is an outstanding fact. It surely needs an explanation from the general angle of tuberculosis epidemiology. If it is true that the prevalence of *fatal* lesions, as measured by the death rate from tuberculosis, has progressively diminished in the general population, then in our opinion only a few explanations seem to be left.

One possibility is that tuberculosis has changed its character as an epidemic involving the virulence of the bacillus and the fatal outcome of the disease. The progressively diminishing death rate could be explained on this basis. It would mean: apparently no diminution of the spread of the disease, but a continuing diminution of its severity. There do exist examples in the history of epidemics of an infectious disease changing as to case fatality. For instance, scarlet fever very definitely has lost, in our lifetime, much of its formerly dreaded character, while the spread of the disease has hardly diminished very much. But all in all, the pathologist as well as the epidemiologist would hesitate to compare the pathological-anatomical feature and the epidemiological course of an acute disease like scarlet fever or measles, which in the majority leave no visible signs on the attacked body, with the very chronic course of tuberculosis which, in practically all cases, destroys the cells and organ tissue more or less locally and, therefore, leaves constant scars. A more adequate example, perhaps, would be that of leprosy, a chronic infectious disease like tuberculosis and, in addition, one that resembles it in bacillary and clinical aspects. Why this chronic infectious disease has ceased to exist as an epidemic among European nations we do not know. It may be that the steady selection through the deadly attack and the enforced isolation during the middle ages up to the present has played a rôle in the disappearance of this plague. Then, the present generations would differ from former ones in their disposition or susceptibility for leprosy. The coming and disappearing of epidemics still to-day leaves many a question unsolved; it is certainly not only the bacillus or the virus that determines the course of an epidemic. The constitutional make-up of the host is another decisive element in the pathological outcome of each disease (Martius, Bauer, etc.).

In the case of tuberculosis the change of its epidemic character does not seem to be the proper explanation. At least not from an experimental point of view regarding the virulence of the tubercle bacillus. As far as animal experiments are conclusive proofs for the characterization of a human disease, present-day tubercle bacilli, cultivated from the human body, are just as virulent as they were sixty years ago when Robert Koch was first able to isolate them. There is, then,

the second alternative to be discussed. If it is not the bacillus, it might be the invaded human body which has changed its constitutional disposition. Such a transition from a more susceptible to a less susceptible status of the present generation is not entirely out of the question. It would parallel the course of leprosy through the centuries.

The steady weeding out of the tuberculous from the population through high death rates in the past could have left a remainder of the population more resistant, or less susceptible, to tuberculosis. That such a differential susceptibility towards tuberculosis does exist even in related family members, such as nonidentical twins, or common sibs, or spouses who have been in close contact and the same environment for years, could be shown again in a new survey on mortality in husbands and wives, brothers and sisters (Wolff and Ciocco (7)). Thus biological selection would afford another explanation of the present phenomenon; it probably has a certain meaning in the decline of the death rate and the epidemiological course of the disease as assumed by many earlier writers since Pearson (8).

Whether it is possible to explain the low death rate of the present, in spite of a high percentage of old healed lesions, by a change of constitutional susceptibility is a somewhat different question which cannot easily be answered. It will be still more difficult to explain the difference in autopsy findings between Hagerstown and Baltimore in this way, namely, by a differing constitutional stock of the respective populations. The high percentage of lesions at autopsy, anyway, shows that a large part of those who died of other diseases—in Hagerstown and still more in Baltimore—is or was attacked by tuberculosis. The time factor complicates the problem, but these lesions may represent a potential source of infection whenever external conditions turn to the worse. The low and steadily lowering death rate, on the other hand, indicates that more and more of the infected escape the deadly issue and thus continue to diminish the open sources "effective in spreading the tubercle bacillus" as Frost (9) has already pointed out.

Finally, there is a third possibility left to explain the discrepancy between a steadily falling death rate and an appreciably slower downward trend of old lesions. The striking phenomenon could be explained as the mere result of therapy in the broadest sense, medical treatment as well as improvement of other environmental conditions. If a change of virulence can be excluded and a change of constitutional susceptibility is disregarded, then the presence of almost 100 per cent healed lesions as in the city of Baltimore would necessarily mean that in our time four to five times as many infected adults have been cured from tuberculosis as in the days of Naegeli and Opie.

The decrease of the death rate from tuberculosis is a well established fact in many parts of the world. What the causes of this gratifying decrease are is another thing not too simply explainable. Our future efforts to eradicate the disease or prevent it from the beginning will be based on evaluating these causes. If it holds true that in other large cities almost the total adult population shows tuberculous lesions at autopsy, it would mean a still greater medical and social success than indicated by our Hagerstown observations. The newer tuberculin

findings show a decrease in positive reactions and thus seem to be in accordance with our results. But on the other hand, their pathological meaning is less significant and more contradictory than direct autoptic observations. Not even the meaning of a positive tuberculin reaction has been clarified, nor the question whether it is desirable or not as a signal of some kind of acquired immunity. Therefore, we fully agree with Carnes, who at the suggestion of Rich published his report, when he emphasizes (as we did in our first report) that more pathological-anatomical surveys should be conducted in other places of the United States. "It is evident," he writes ((2) p. 103), "that the value of tuberculin surveys in determining the incidence of infection under the conditions prevailing today is subject to doubt. More certain information must be gotten by the original method of postmortem anatomical search."

Our conclusions, nevertheless, are based on the autoptic findings in Hagerstown as compared with former investigations from other parts of the world and obtained by the same methods as the classical observations of Naegeli. The apparent reduction of tuberculous lesions at autopsy, then, invites still another and rather logical explanation of the epidemiological facts, provided that the reduction will be verified from other places. It would be desirable indeed to obtain more pathological-anatomical information within the United States. It would be of great interest, in particular, to know more about the geographical prevalence of tuberculous lesions in different states and to clarify the question of the present frequency by comparing, for instance, autoptic findings in Utah, Wyoming, Nebraska with extremely low death rates (in the last years hardly 15 deaths per 100,000 population), to those in Maryland, Kentucky, Tennessee, Arizona, which still exhibit death rates from tuberculosis many times higher. It should be possible to standardize the autoptic methods and to find the pathologists trained in performing them at various places.

The present report, covering a period of six years from a middle-town and semi-rural population, does not essentially change our former findings. But it is now based on a reasonably large number for such a population group, that is, on a total of 440 autopsies. Among them the percentage of tuberculous findings has risen to 55.2 (against 48.4 in the first report on 165 autopsies). Since the main purpose of this follow-up report is the publication of the new figures, it is not necessary to go into a more meticulous statistical-epidemiological analysis and a repetition of the original discussion with slight corrections due to the new results. It might be underlined, however, that all three factors determining the outcome of the single case, the specific factor of the virus, the constitutional factor of the host and the environmental factor of human society, also determine tuberculosis as a mass phenomenon and ought to be considered in the discussion.

It should be clear from the total series of our autopsies that the frequency of tuberculous lesions, when compared with Naegeli's and Opie's results, has appreciably lessened, to almost half in all reported ages. From such a reduction of positive findings at autopsy we are induced to conclude that in a present-day description of our population only half of the adults show definite signs of more or less healed tuberculous infection. Including the children (under twenty years),

the percentage goes down to 45.2 for the combined survey of 440 autopsies. The proportional reduction during childhood is in good accordance with observations of Wollstein and Spencer (10) from the New York Babies Hospital since the turn of the century (see our first report). Such a reduction of the potential sources of infection would indicate a real prevention of the disease, and thus possibly a success of preventive medicine. If, in addition, the death rate from tuberculosis has still further decreased, the infected part of the population, as marked by positive autopsy findings, must necessarily have reduced its case fatality too. This can be attributed to medical therapy including hospitalization and other social-environmental influences, if epidemiological changes can be excluded as described in the earlier part of the discussion. It is quite evident that the case fatality rate of the infected must have diminished proportionally, the higher the proportion of the infected people at autopsy has been found to be.

The time element complicates the problem. However, that we are dealing with a true decrease in the spread of tuberculosis, not with a purely statistical change of qualities, becomes obvious if one realizes that the present high frequencies found in the age brackets fifty years and over only reflect the *former* frequency of infection but do by no means signify an increased exposure rate of the present population with increasing age. The time factor in a chronic infection like tuberculosis can hardly be taken care of through autopsy records. The people who die, for instance, at the age of fifty, and show tuberculous lesions at autopsy, may have been infected ten, twenty, thirty or forty years ago. Nothing exact can be said about this from present autopsy examinations, except that the great majority of them have been saved from tuberculosis death but have died from other causes. Almost the same was the case even at a time when the death rate from tuberculosis was as high as 200 or more per 100,000, which means that 2 out of 1,000 in a generally infected population have died of tuberculosis.

However, as was already pointed out in our first communication, even under the much lower death rates of the present and under the still more favorable conditions of a semirural population with a lower tuberculous *Durchseuchung* in all ages, a sudden flare-up of the open disease is not beyond the possible eventualities. The influence of total war upon the epidemiology of tuberculosis cannot yet be predicted, although the downward trend of tuberculosis mortality seems to continue—at least in this country, far from the scene of actual combat and far from a direct impairment of external conditions.

#### SUMMARY

1. The second survey of autopsy material in a semirural population (Washington County Hospital, Hagerstown, Maryland) covers 275 additional autopsies available for the study of frequency of tuberculous lesions. Together, the former and new series amount to 440 postmortem examinations.

2. The index of infection with tuberculosis as gathered from these autopsies is again low in childhood and adolescence, less than 10 per cent; it increases in the brackets between twenty and fifty years to slightly below 50 per cent and reaches, in the older age groups, values approaching 70 per cent.

3. Compared with the findings of Naegeli at the turn and of Opie at the beginning of the century, the present values from Hagerstown are about halved for the ages up to fifty years. Such a reduction of tuberculous lesions at autopsy would indicate the complete escape from infection with tuberculosis, which, however, seems to hold true only for population groups outside of large cities.

4. The fact that the death rate from tuberculosis has decreased to a higher degree than the amount of tuberculous lesions indicates, in addition, an appreciable reduction of the case fatality rate among the infected people. This reduction of case fatality must be proportionally the higher, the less the tuberculous *Durchseuchung* of the population as shown by autoptic findings diminishes. If a change in virulence of the epidemic and a change in constitutional disposition can be excluded, the lessening of the fatal issue of tuberculosis must necessarily be attributed to modern therapy.

5. In spite of the apparent success of the battle against tuberculosis waged in the last forty years, even the favorable frequency figure of lesions from Hagerstown proves that under reversed conditions a sudden flare-up of tuberculosis is by no means beyond possible eventualities.

#### SUMARIO

1. Este segundo estudio de material autopsico de una población semirrural (Hospital del Condado de Washington, Hagerstown, Maryland) comprende otras 275 autopsias disponibles para el estudio de la frecuencia de las lesiones tuberculosas. Las dos series comprenden 420 estudios autopsicos.

2. El índice de infección tuberculosa según lo expresan esas autopsias, resulta nuevamente bajo en la infancia, y en la adolescencia: menos de 10 por ciento; aumenta en las edades de 20 a 50 años a algo menos de 50 por ciento, y alcanza en los grupos de mayor edad cifras que se aproximan a 70 por ciento.

3. Comparadas con los hallazgos de Naegeli al final del último siglo y de Opie al comienzo del siglo actual, las cifras actuales de Hagerstown vienen a representar la mitad hasta la edad de cincuenta años. Esa disminución de las lesiones tuberculosas en la autopsia indica una indemnidad completa lo que sin embargo sólo parece rezar con la población de fuera de las grandes poblaciones.

4. El hecho de que la mortalidad tuberculosa haya disminuído más que el coeficiente de lesiones tuberculosas indica, además, una baja apreciable del coeficiente de morboletalidad entre los infectados. Esa baja debe ser proporcionalmente mayor mientras menos disminuye la "Durchseuchung" tuberculosa de la población según revelan los hallazgos autopsicos. Si pueden excluirse un cambio de la virulencia de la epidemia y una alteración de la predisposición constitucional, hay que atribuir forzosamente a la terapéutica moderna la disminución en el desenlace letal de la tuberculosis.

5. A pesar del éxito aparente de la lucha librada contra la tuberculosis en los últimos 40 años, hasta las cifras favorables para las lesiones, que provienen de Hagerstown, demuestran que, de cambiar las circunstancias, no está, ni mucho menos, fuera de lo posible una súbita exacerbación de la enfermedad.

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# PATHOGENIC COMPONENTS OF THE TUBERCLE BACILLUS<sup>1</sup>

## A Discussion of Recent Advances in Certain Fields of Tuberculosis Research and Postulation of Specific Component of the Tubercle Bacillus Determining Virulence

GARDNER MIDDLEBROOK<sup>2</sup>

It would be a waste of time to expound upon the importance of the "little red devil" in his competition with man, but we hope to present some idea of what man is doing in a few corners of his side of the battlefield in an attempt to find vulnerable points of attack in his hardy opponent. We shall discuss those aspects of tuberculosis research in which there is wide-spread interest at present: chemotherapy of tuberculous infections with sulfonamide-like compounds; enzymes in tuberculosis; and the immunology of tuberculosis, with the postulation of a specific chemical component of the tubercle bacillus which determines its virulence.

### I. Bacteriostasis of the Tubercle Bacillus and Chemotherapy of Tuberculosis with Sulfonamide-like Compounds

The sulfonamide and sulfonamide-like compounds, defined as those whose bacteriostatic effects are antagonized by para-amino benzoic acid, have come into prominence not only in the treatment of various acute infections but also in the possibility of their use in the treatment of tuberculosis. There is very convincing evidence (1 to 13)<sup>3</sup> that experimental infections with virulent tubercle bacilli in various animals can, under certain conditions, be markedly retarded in their progress, if not "cured." It is becoming more and more evident that they cannot "cure" tuberculosis in the sense that the host's body is rid of all living tubercle bacilli, but the term "cured" is known by most students of infectious diseases, especially of tuberculosis, to be a dangerous term, and the importance of any agents which can inhibit the characteristic progress of a tuberculous process must be obvious to the clinician; and, this, it can safely be stated, these drugs most definitely do, at least in the experimental animal. (See table 1.)

We shall consider in order the following topics:

- 1: The fundamental physico-chemical characteristics of the sulfonamide-like agents.
- 2: Their mechanism of action *in vitro* with variables of drugs, organisms and medium which determine this action.

<sup>1</sup>This paper was presented, in part, before the Boylston Medical Society, Harvard Medical School, Boston, Massachusetts, on April 15, 1944, with Dr. Bruno Gerstl, Yale Medical School, and Dr. Rene Dubos, Harvard Medical School, discussers.

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<sup>3</sup>The first report in the literature of success in retarding the progress of tuberculosis in experimental animals with a sulfonamide was that of A. R. Rich and R. H. Follis, Jr., Bull. Johns Hopkins Hosp., 1938, 62, 77.

3: Factors determining their activity *in vitro*.

4: Drug-fastness and general considerations.

# PHYSICO-CHEMICAL CONSIDERATIONS OF BACTERIOSTASIS OF THE TUBERCLE BACILLUS BY SULFONAMIDE-LIKE COMPOUNDS

The general formula for sulfonamide-like compounds (defined as those whose bacteriostatic activities are antagonized by para-amino benzoic acid) may be represented as in figure 1.

R— shown by *in vitro* experiments, must not be too firmly bound to N, and any compound showing activity *in vitro* or *in vivo* always shows more activity when this R group is removed, but the presence of certain R groups seems to reduce the toxicity for the host without proportional reduction of

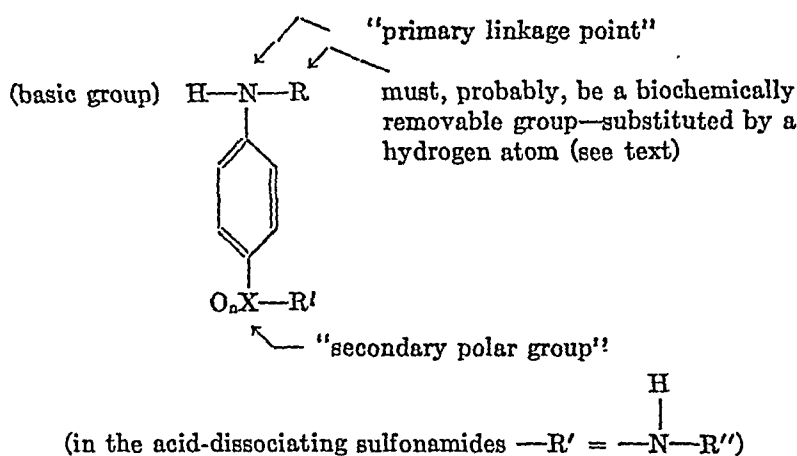


FIG. 1. Schematized representation of the fundamental formula of all the sulfonamide-like bacteriostatic agents.

chemotherapeutic activity. R must not be too hydrophobic for it may so reduce solubility to the extent that:

(1) Hydrolysis cannot be accomplished *in vitro* or *in vivo* because of insufficient molecular contact with hydrolytic agents.

(2) It prevents by its hydrophobic nature, by its specific structure, or its mere size the essential primary linkage of the amino nitrogen with the specific locus on or within the susceptible organism. Because of the failure to develop chemical methods for determining the relative amounts of free diaminodiphenylsulfone and its N derivatives, however, no definite statements as to the activity of these derivatives *in vitro* or *in vivo* can be made; it cannot be definitely stated that they do not penetrate the peripheral structures of the tubercle bacillus.

X—it is known, need not be a sulfur atom; indeed it has been shown that some bacteriostatic activity may be present with other heavy atoms such as selenium, tellurium (14), arsenic, phosphorus (15) and even carbon (diamino-benzophenone is active and antagonized by para-amino benzoic acid (16)).

n— depends upon the valence of the heavy atom, X.

R'—in the sulfonamides consists of "NH-R'" making this an acid dissociating group, and thus determining, to some extent, the bacteriostatic activity of the compound, first because it reflects the electro-negativity of the "XO<sub>n</sub>" group, and, second, probably influences the permeability of the compound for the peripheral structures of the susceptible organism, as will be discussed. R" also influences the electro-negativity of the "XO<sub>n</sub>" group; it also influences the hydrophobic character of the whole compound with the same results as described for R; and it is evident from some experiments that its particular structural similarity to another metabolite than para-amino benzoic acid (thiamin, nicotinic acid, etc.) may play a part unrelated to and in addition to the anti-para-amino benzoic acid effect of the rest of the molecule in contributing to bacteriostasis in certain concentrations of the compound (17).

The "receptor" theory of Ehrlich, as modified in the light of more recent knowledge by Dubos (18) and others, can be of some assistance in the explanation of the mechanism of action of the sulfonamide-like bacteriostatic agents and, although some specific knowledge is lacking, certain ideas as to many factors involved in bacteriostasis by sulfonamide-like compounds can be formulated.

Since polar groups (dissociating and nondissociating) are generally considered the biochemically important groups for organic agents influencing metabolic functions, let us consider these groups in the sulfonamide-like agents.

The first polar radical, a dissociating group, basic in character, is the free para-amino group. This is obviously the more important group for the "receptor" (which must be an acid-dissociating group) at the locus of action in the bacterial cell, because it must be present and must not be blocked by an R group. This may be called the "primary linkage point" (for bacteriostasis, some form of combination of this amino group must occur with the specific locus in or on the surface of the susceptible microorganism); the XO<sub>n</sub>-R' group we shall term the "secondary polar group"—its physico-chemical properties, as we shall attempt to elucidate, determine the affinity of the compound (and, therefore, its toxicity) for the specific enzyme system whose normal function it inhibits; this system, probably, is important in and only in the reproduction of the bacterial cell for bacteriostatic concentrations of the agents do not disturb other functions of the individual bacterium until the agent in higher concentration begins to act as a more or less nonspecific toxin, when the metabolism of the cell, as measured by respiration, stops, with death of the cell. Thus, the sulfonamide-like agents are bacteriostatic in low concentrations—their linkage with the postulated enzymic protein receptor is specific and reversible, and at much higher concentrations bactericidal—their less specific linkage with other loci in the cell more or less promptly affects its viability. These higher concentrations are probably never attained *in vivo*.

We have mentioned that one of the important factors which determine the bacteriostatic activities of these compounds is the electro-negativity of the XO<sub>n</sub> group. This electro-negativity can be calculated for any one of the sulfonamide-like compounds (19, 20) and the following deductions made:

(1) The acid constants ( $pK_a$ 's) of the dissociating compounds furnish an indirect measure of the negative character of the  $XO_n$  groups (see figure 2).

(2) The  $XO_n$  group is more negative in the ionic species which is therefore much more active (in the acid-dissociating sulfonamides like sulfadiazine and sulfathiazole) than the unionized form at the enzyme surface.

(3) The more acidic (the lower the  $pK_a$ ) the sulfonamide is, the less negative is the  $XO_n$  group of both the ionic and the molecular forms.

(4) The  $XO_n$  group (the  $SO_2$  group, when sulfur is the heavy atom, as it is in the sulfonamide-like compounds more completely discussed here) of the sulfones is probably highly electro-negative because of a lack of a nearby acid-dissociating amide group and because of resonance effects (20). The sulfones seem to be

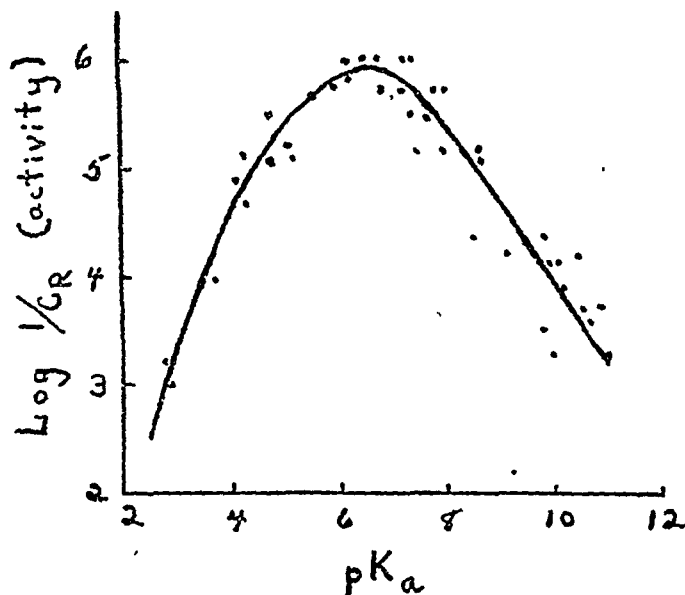


FIG. 2. Distribution of sulfonamides according to the  $pK_a$ 's of their acid-dissociating groups and their bacteriostatic activity for *E. coli* at pH 7.  $C_R$  represents the minimum molar concentration necessary to cause bacteriostasis. (Ref. 15.)

specifically more active against the tubercle bacillus (21) for reasons which we shall soon discuss.

It has been generally established that cell membranes are more permeable for the unionized forms of dissociating compounds (22). Now it is evident that the lower the  $pK_a$  of the sulfonamide, the more dissociated (ionized) it will be at pH 7, at which pH it is usually tested *in vitro* for bacteriostatic activity. Therefore, one would expect that this would become a limiting factor for sulfonamide activity and that is evident from examination of figure 2. Sulfonamides arranged according to their  $pK_a$ 's show increasing activity with diminishing  $pK_a$ 's down to about 7; from this point on, a diminution in  $pK_a$  diminishes activity because the factor of increasing proportion of ions to molecules comes into play and this (in addition to the fact that the more acidic the dissociating group, the less electro-negative are both the ionic and molecular species) more than compensates for

what advantage the potentially greater concentration of active ionic species in the bacterial cell (at pH 7) should afford the bacteriostatic compound at the locus of action.

If these explanations of the variation of bacteriostatic activities with degrees of dissociation are true, then one would predict that any particular sulfonamide should show characteristic changes of activity with changes in the pH of the medium. There are two dissociating groups in any "true" sulfonamide, the acid-dissociating amide group and the basic dissociating para-amino group; measurements of the  $pK_b$ 's of the para-amino groups have shown (19) that they vary only slightly among all the sulfonamides and range about  $pK_b$  12. One would expect, for instance, that in the case of sulfadiazine with a  $pK_a$  of 6.5, as the pH of the

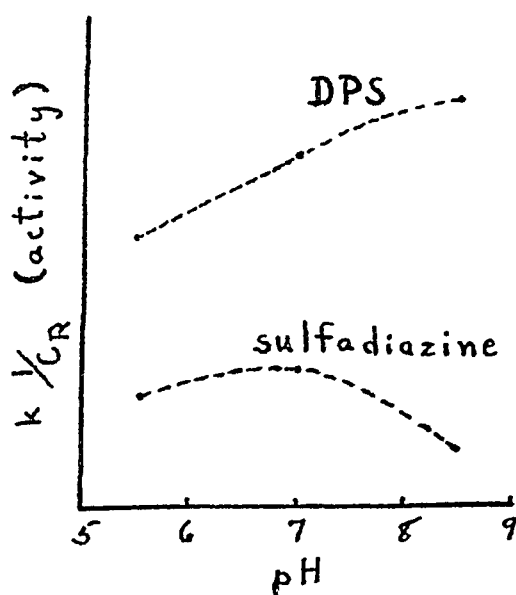


FIG. 3. Effects of the pH of the medium on the bacteriostatic activities of diaminodiphenylsulfone and sulfadiazine for the tubercle bacillus. (Ref. 25.)

testing medium were raised, there would be at first a slight increase in bacteriostatic activity as the basic dissociation of the compound is depressed (and for another reason to be discussed shortly), rendering the compound more easily permeable through the peripheral structures of the bacterial cell, but that after this rise there should be a maximum near the  $pK_a$  of the compound and then a decrease in activity as the acidic dissociation becomes increased. This is exactly what happens with sulfadiazine when tested against the tubercle bacillus H37 in the available pH range 5.5 to 8.5 (figure 3) (25).

According to this theory relating activity to degrees of dissociation at any particular pH, one should expect that those compounds which lack an acid-dissociating group, like diaminodiphenylsulfone, would tend to increase in bacteriostatic activity with increasing pH of the test medium over a wide range; and

this seems to be the case: diaminodiphenylsulfone shows increasing activity against the tubercle bacillus in the range which can be tested, pH 5.5 to 8.5 (figure 3). It should be stated that, inasmuch as it can be calculated that there is very little change in the proportion of ionic to molecular forms in the range of pH 5.5 to 8.5 for weak basic groups with  $pK_b$ 's between 10 and 12, and since there is probably a small amount of para-amino benzoic acid in the medium from the inoculum, some of this increase in activity could be attributed to the increasing acidic dissociation of para-amino benzoic acid with its diminished penetration into the cell to compete with the sulfonamide-like agent, allowing an apparent increase in the bacteriostatic activity of the inhibitor. There is experimental evidence to support this contention which fits well with our general theory (23).

Moreover, it has been observed (25) that there is a greater difference between the bacteriostatic activities of sulfathiazole and sulfadiazine against the tubercle bacillus at pH 7 than against other microorganisms. It is possible that this is due to peculiar specificities of their different  $R''$  groups, but, according to our theories, it can be explained by the specifically greater resistance of the tubercle bacillus to the penetration of ions through its peripheral structures, inasmuch as the  $pK_a$  of sulfathiazole is about 7.1 while that of sulfadiazine is about 6.5, allowing sulfathiazole to be much more undissociated than sulfadiazine at pH 7 and therefore more active.

These conceptions and the observations that they explain so adequately certainly justify the assumption that the susceptible locus of action of the sulfonamide-like compounds is within the peripheral structures of the bacterial cell. This assumption, furthermore, may explain why the tubercle bacillus with its rather selectively permeable peripheral structures (its resistance to the lethal effects of strong acids and bases is well known) is relatively more susceptible to the non-acid-dissociating sulfones and less susceptible to acid-dissociating compounds like sulfathiazole and sulfadiazine than are other susceptible microorganisms (19, 21). In general, however, the slow-growing acid-fast organisms are less susceptible to sulfonamide-like agents than are other organisms for which these compounds are used with good clinical results, perhaps because they synthesize more para-amino benzoic acid than other sulfonamide-susceptible organisms (24).

Thus, the generally accepted theory relating sulfonamide activity to the electro-negativity of the  $XO_n$  group and pointing to the ionic species of the acid-dissociating compounds as being the active bacteriostatic form of these agents should, in the light of the investigations of others and of these observation on the tubercle bacillus (25 to 29), be modified to include the important assumption that the peripheral structures of bacterial cells are more permeable for the unionized than for the ionized forms of sulfonamide-like agents, although once within the cytoplasm the undissociated form of the acid-dissociating compounds ionizes according to the equilibrium equation at pH 7 to give the more active, highly electro-negative, ionic form (figure 4).

In view of these physico-chemical considerations, it does not seem unwarranted to predict that the bacteriostatic activities of any particular series of chemical

agents whose mechanism of action depends upon interference with specific metabolic processes within the peripheral structures of susceptible organisms will *tend* to be higher for those compounds which are less dissociated at neutrality—and particularly so in the case of slow-growing, acid-fast organisms.

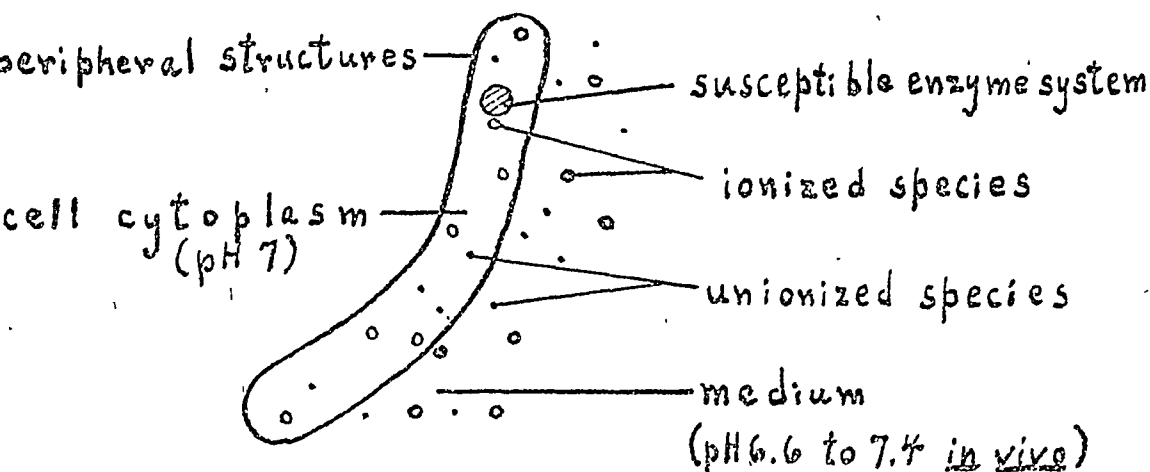


FIG. 4. Diagrammatic representation of bacteriostasis of the tubercle bacillus by acid-dissociating sulfonamide, based on the assumption that the agent must penetrate the peripheral structures of the bacterial cell to reach the susceptible enzyme locus within the cell cytoplasm, and that these structures are more or less impermeable to ions. The number of the highly active (see text) ionic species within the cytoplasm will be determined by: (a) the number of unionized molecules of the compound available for penetration into the cytoplasm which will, in turn, depend upon the degree of ionization of the compound at the pH of the medium; (b) the degree of dissociation of the compound at pH 7, the presumed pH of the bacillary cytoplasm, regardless (within vital limits) of the pH of the medium.

#### SUMMARY OF FACTORS DETERMINING ACTIVITY IN VITRO

In summary, then, the bacteriostatic activities of any of the sulfonamide-like agents are functions of many variables, probably in the following order of importance:

1. The presence and quantitative metabolic importance of the specifically susceptible biochemical structure in the bacterial cell. In this connection it is worth mentioning that it is not yet certain whether these agents act by interfering with the utilization of para-amino benzoic acid as an essential intermediary metabolite or whether the competition is more of the nature of what is termed an "ionic exchange" where two substances, separately toxic in some phase of cell physiology, nullify each other's effects when mixed in proper balance (30), for it is known that para-amino benzoic acid alone is bacteriostatic in somewhat higher concentrations than sulfonamides (10). (In the case of some drug-fast organisms the increased sulfonamide resistance seems to be due to the ability of the bacteria to synthesize more para-amino benzoic acid to compete with the sulfonamide (31).)

2. The possession of a fundamental structure similar to para-amino benzoic acid and more specifically of the structural type schematized in the general formula in figure 1.

3. The electro-negativity of the  $XO_n$  group.

4. The degree of dissociation of the para-amino group and of the  $O_nX-NH-R$  group, if the compound be a "true" sulfonamide, which determines the permeability of the peripheral structures of the bacterial cell for the compound. (The degree of dissociation of the amino group may be important at the enzyme surface in the cell, but no means of studying this have been developed (31).)

5. The relative freedom of the amino nitrogen ("primary linkage point") to combine (adsorb ?) with the susceptible locus in the cell.

6. The presence or absence of particular  $R'$  or  $R''$  groups which may *per se* have antibacterial activity unrelated to para-amino benzoic acid antagonism (31).

7. The character of the growth medium with regard, in particular, to the presence or absence of antagonists, to the pH of the medium, and to the presence of other agents which may potentiate the effects of sulfonamide-like agents (31).

#### ACTIVITY IN VIVO

Since the bacteriostatic activity of any particular antibacterial agent *in vitro* is not, in the final analysis, a necessary criterion of its chemotherapeutic value, one must consider the following factors in a general view of the problem:

A: Toxicity of the agent for the host, including practical considerations of clinical application, such as route and ease of administration over a long period of time, antigenicity, etc. (31).

B: Activity of the agent in the host as influenced by:

1. Concentration of active agent molecules in the vicinity of the reproducing, "invading" bacterial cells, as determined in turn by many variables:

(a) Route of administration of the drug. (Inhalation techniques have not been given adequate experimental or clinical trials in pulmonary tuberculosis (8, 32).)

(b) Predominant locus of multiplication of the bacteria-intracellular or extracellular. (The importance of intracellular multiplication of tubercle bacilli should direct attention again to the permeability of cell membranes for the antibacterial agent in tuberculosis (31).)

(c) Rate and locus of hydrolysis of the drug to release active molecules from purposely conjugated drugs such as promin, diasone, and "N-phosphoryl" diaminodiphenylsulfone. (The possibility that certain enzymes may be particularly active in and about tuberculous lesions may be guides to the synthesis of conjugated drugs of low host toxicity and high chemotherapeutic activity because of specifically rapid release of free, active agent molecules in these foci, for example, increased phosphatase (33).)



- (d) Inactivation of the agent by binding with plasma proteins, biochemical conjugation, breakdown, or general chemical instability at the pH and temperature of the host's tissue fluids (31).
  - (e) Rate of excretion of the drug (31).
2. Presence of antagonists (such as para-amino benzoic acid, etc., for sulfonamide-like agents) from tissue necrosis. (The greater tendency toward liquefaction, cavitation, and continued purulent discharge (presumably containing para-amino benzoic acid in quantity (31)) in human pulmonary tuberculosis compared with tuberculosis in the guinea pig may be a factor in the superiority of sulfonamide-like chemotherapy in the latter.)
  3. Although not yet specifically encountered in chemotherapy, one should keep in mind the possibility that a chemical agent, inactive *per se in vitro*, may be biochemically synthesized *in vivo* into an active antimicrobial agent. This is an obvious reason (among others) for investigators not to trust *in vitro* tests too exclusively in their search for new chemotherapeutic agents.

The state of our knowledge concerning most of these *in vivo* factors is inadequate to make such generalizations relating chemical structure to these variables as are possible concerning bacteriostatic activity *in vitro*. It is obvious that the pharmacological effects on the host may be the resultant of many variables and a drug may have pharmacological activity at many loci. It will suffice to name these loci according to present observations; their biochemical identification may in the future allow the reduction of toxicity for the sulfonamide-like compounds without interfering with their bacteriostatic activities (34, 35, 36).

1. Hematopoietic system: Principal toxic effects of the "sulfone" derivatives in man (300 to 400 cases from the literature):
  - (a) Reduction of red blood cells and hemoglobin, usually gradual, and always reversible.
  - (b) Formation of methemoglobin during early period of administration (37).
  - (c) Increase in white blood cells accompanying the reduction of red blood cells and reversible by the same technique, in addition to cessation of drug administration. (Rare leucopenia, never serious as yet (37).)  
(Whole dried liver and certain liver extracts by mouth have been demonstrated to prevent and reverse the results of the toxic effects on this system (34) in rats at least.)
2. Kidneys: Some of the sulfonamides, especially those which have low water solubilities and are not conjugated into more soluble forms, produce renal concretions and may have a more specific toxic effect on tubular epithelial cells (31, 38).
3. Immunological system: The sulfonamide-like drugs tend to become conjugated (bound)—by their amino groups, in our opinion—with plasma proteins and thus act as partial antigens, which results in many allergic manifestations. Desensitization procedures can be instituted in the more chronic diseases to prevent these signs of toxicity (35).

4. Nervous system: Many symptoms and signs have been produced by or, at least, attributed to the sulfonamides-like drugs and psychotic symptoms and signs seem to develop particularly during the maintenance of high blood levels (31).
5. Gastro-intestinal tract: Nausea and sometimes vomiting have been encountered with most of the sulfonamide-like drugs, and especially during the early period of their administration to tuberculous patients (37). The mechanism of this is not clear (31).

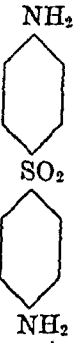
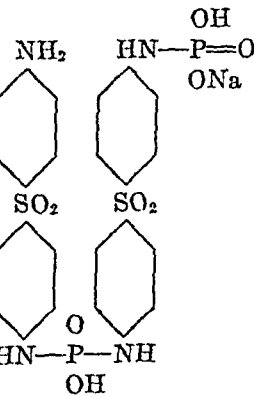
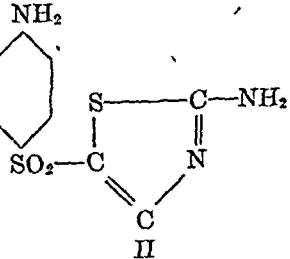
It is evident from experimental animals and humans that a certain degree of tolerance is developed when therapy is continued. This may be considered analagous to the development of drug-resistance by susceptible microorganisms (37, 39).

The only sulfones which have been given clinical trials in human "acid-fast" infections are promin and diasone (see table 1). The results of these investigations (35, 37, 40 to 42) have been questionable because the number of patients treated was small and the techniques of control were inadequate, but there is a suggestion from the few reports that both these compounds have a favorable influence on early leprotic and tuberculous lesions, and that further clinical investigation of compounds like promizole and particularly the "N-phosphoryl" derivative of diaminodiphenylsulfone should be made. Unfortunately, no follow-up reports on patients who have had months of chemotherapy have been made available. The evidence from experimental chemotherapy in guinea pigs indicates that this should be an essential part of clinical evaluation of these agents, inasmuch as many of the guinea pigs, which on chemotherapy had outlived all the untreated control animals, ultimately developed fatal tuberculosis after cessation of chemotherapy (12).

As for the possibility that the sulfonamide-like agents have a chemotherapeutic action in tuberculosis other than by means of a direct effect on the reproductive mechanism of the tubercle bacillus, there is no definite evidence. It has repeatedly been demonstrated that, in the case of other sulfonamide-susceptible infections, bacteriostasis is the only mechanism by which the sulfonamides modify infectious diseases and there is no explicit evidence to lead one to believe that there are additional mechanisms in tuberculous infection, except in the interesting case of promizole (see table 1) which has an effect on the thyroid similar to, but one-half as potent as, thiouracil (43); this probably lowers the metabolic rate of the guinea pig and may, by reducing the motor activity of the animal, or by some as yet undiscovered hormonal mechanisms, assist in retarding the progress of its tuberculous infection; these possibilities obviously deserve further investigation. Nevertheless, there is no evidence that the sulfonamide-like agents have any direct effect on classical immunological mechanisms.

It has been well stated "that to interfere with the pathogenic career of a parasite it is not indispensable to exert on it an injury affecting its viability; it is sufficient to attack some component or product of the cell which conditions pathogenicity" (18); certainly a metabolic system essential for the reproduction of the bacterial cell can be considered an important "component of the cell which conditions pathogenicity."

TABLE 1  
Sulfonamide-like compounds in tuberculosis\*

	BACTERIO- STASIS IN VITRO AT pH 7	MAXIMUM THERAPEUTIC EFFECTIVE- NESS IN GUINEA PIG	ADEQUATE BLOOD LEVEL FOR MAXIMUM THERA- PEUTIC ACTIVITY IN GUINEA PIG	TOXICITY RATIO† GUINEA PIG/HUMANS (ESTIMATED)
 NH <sub>2</sub> SO <sub>2</sub> NH <sub>2</sub> diaminodiphenylsulfone (DPS)	1.5 mg. per cent	++++	free total, 4.0- 5.0 mg. per cent	Stated to be too toxic for man (Long and Bliss 1939)
 NH <sub>2</sub> OH HN—P=O ONa SO <sub>2</sub> SO <sub>2</sub> HN—P—NH OH N-phosphoryl DPS	5-8 mg. per cent	++++ at one third of the maxi- mum toler- ated dose for guinea pig	6-8 mg. per cent	Not yet reported for man
‡ NH <sub>2</sub>  SO <sub>2</sub> —C    S—C—NH <sub>2</sub>          C    N C H	No in- hibi- tion at 10 mg. per cent	+++	1.5-4.5 mg. per cent, 2.6 average	2.6/2.3 = 0.9

\* Given in order of effectiveness against tuberculosis of human strain organisms in guinea pigs. All of these compounds are antagonized by small amounts of p-amino benzoic acid *in vitro*.

† The higher the ratio the more toxic for man than for the guinea pig; derived by comparing the blood concentrations which give approximately equivalent toxic effects.

‡ Note marked discrepancy between bacteriostatic concentration of promizole and blood level and see text concerning its effect on the thyroid. This effect has been confirmed and DPS has been found to have only slight thyroid activity. (Astwood, personal communication).

TABLE 1—Continued

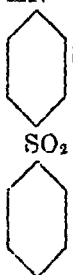
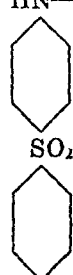
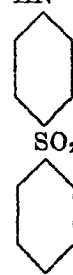
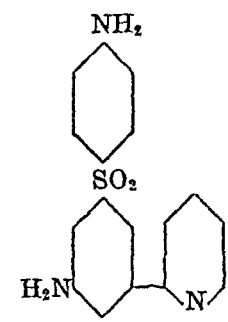
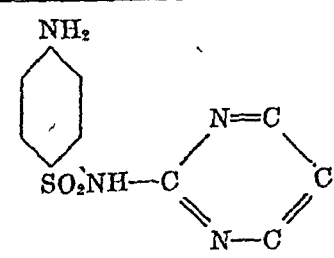
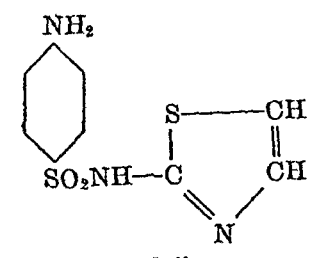
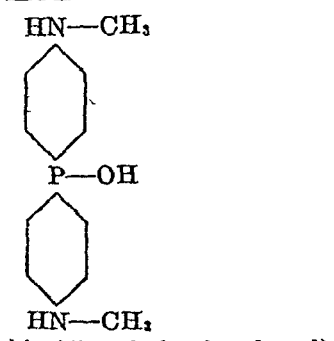
	BACTERIO- STASIS IN VITRO AT pH 7	MAXIMUM THERAPEUTIC EFFECTIVE- NESS IN GUINEA PIG	ADEQUATE BLOOD LEVEL FOR MAXIMUM THERA- PEUTIC ACTIVITY IN GUINEA PIG	TOXICITY RATIO† GUINEA PIG/HUMANS (ESTIMATED)
$\text{HN}-\text{CH}-(\text{CHOH})_4-\text{CH}_2\text{OH}$  $\text{HN}-\text{CH}-(\text{CHOH})_4-\text{CH}_2\text{OH}$ "promin"	20-30 mg. per cent	+++	Stated to be from 5-10 mg. per cent	1.3 ?
$\text{HN}-\text{CH}_2-\text{SO}_2\text{Na}$  $\text{HN}-\text{CH}_2-\text{SO}_2\text{Na}$ "diasone"	6-9 mg. per cent	+++	1.5-4.0 mg. per cent with 3.0 as an average	1.4 ? Levels attained in man are 0.8-1.7 mg. per cent for a period of four months; varies little with dos- age
$\text{HN}-\overset{\text{O}}{\parallel}\text{C}-(\text{CH}_2)_{10}-\text{CH}_3$  $\text{NH}_2$ N-dodecanoyl, DPS	Not re- ported	++	No determi- nations re- ported	? Not reported for man

TABLE 1—Continued

	BACTERIO- STASIS IN VITRO AT pH 7	MAXIMUM THERAPEUTIC EFFECTIVE- NESS IN GUINEA PIG	ADEQUATE BLOOD LEVEL FOR MAXIMUM THERA- PEUTIC ACTIVITY IN GUINEA PIG	TOXICITY RATIO† GUINEA PIG/HUMANS (ESTIMATED)
 “M6”	Not re- ported	+	No determi- nations re- ported	? Not reported for man
 “sulfadiazine”	6-8 mg. per cent	+	16 mg. free sulfadiaz- ine, for long period	16/8 = 2 ? Known not to be effective in hu- man tuberculo- sis by oral and intravenous routes
 “sulfathiazole”	3-4 mg. per cent	+	Varies from 1-4 mg. per cent free sulfathia- zole but not well re- ported	4/4 = 1 ? Known not to be effective in hu- man tuberculo- sis by oral and intravenous routes
 bis-(dimethylaminophenyl) phosphinous acid	30-40 mg. per cent ? Not well deter- mined	+	Guinea pig level not determined	Not reported for man

## DEVELOPMENT AND IMPORTANCE OF DRUG-FASTNESS

It has often been demonstrated that sulfonamide-susceptible organisms can develop resistance to increasing concentrations of sulfonamide-like compounds, both *in vitro* and *in vivo* (44). The tubercle bacillus seems to be no exception to this rule. There is one report (45) that with the development of resistance to promin the tubercle bacillus becomes less virulent, but this observation has not been confirmed and it is hard to believe, inasmuch as all the evidence concerning other sulfonamide-susceptible organisms conclusively indicates that there are no detectable variations in population virulence characteristics coincident with the development of sulfonamide-resistance. It has been assumed that the rate at which an organism (culture of organisms) can develop drug-resistance is roughly proportional to its rate of growth; thus, the tubercle bacillus is very slow in developing drug-resistance (46). However, there has been frequent repetition of the observation that the sulfonamide-like drugs cannot consistently rid the experimental animal of all tubercle bacilli; this is as one might expect in view of the special means by which a host reacts to the invasion of tubercle bacilli—walling off the organisms protects them from phagocytes as well as it tends to protect the host from the organisms and a sort of symbiosis is the characteristic end-picture under these circumstances. Thus, to “cure” tuberculosis in the sense of ridding the host of all living bacilli after they have been present for a period of time, even if one possessed a sulfonamide-like agent of great bacteriostatic effectiveness, is an unwarranted hope.

The development of drug-resistance without corresponding loss of virulence, therefore, precludes indefinitely long periods of chemotherapy or successful repetition of chemotherapy at subsequent intervals. It also obviously allows the possibility of increasing numbers of hosts infected with initially drug-resistant tubercle bacilli.

It is evident, therefore, that the future of chemotherapy with sulfonamide-like agents is not the rosy picture which unconsidered opinion would have it. And this is as true (if not more true) of the chemotherapy of tuberculosis with the sulfonamide-like drugs as of the chemotherapy of any of the other sulfonamide-susceptible infections. This warning is not meant to discourage further investigation of these or similar bacteriostatic compounds, because it may be that for a few years an active sulfonamide-like agent (in our opinion, necessarily more active than those already given clinical trial) could have a valuable place in the treatment of tuberculosis.

One can hopefully expect the isolation of a microbial product with the biological properties of penicillin—low toxicity for mammalian tissues, reduction of population virulence with the development of drug-fastness—but with effective bacteriostatic activity for virulent tubercle bacilli. This would be, in some senses, a welcome answer to the chemotherapy of tuberculosis, but one should not entertain the hopes that such an agent could reverse the tissue damage already done by previous disease or abruptly terminate the further damage that dead (or inhibited) tubercle bacilli are known to produce. Moreóver, we do not hesitate to

affirm that any merely bacteriostatic agent, chemotherapeutic for tuberculosis, will demand more or less prolonged periods of treatment and probably, in many cases, repetitions of treatment at subsequent intervals.

Undoubtedly, the possibility that two or more antibacterial agents may be more effective therapeutically than individual agents allows the prediction that polychemotherapy may become a prominent technique in the treatment of tuberculosis as well as of other infections (25, 47).

Finally, it seems to us that the problems of most immediate importance for the investigator searching for agents with chemotherapeutic possibilities in tuberculosis are:

(1) The development of adequate chemotherapeutic tests in experimental animals which necessitate only small amounts of chemical agents, in view of the too little appreciated problems of organic synthesis (48).

(2) The development of quantitative techniques for observing bacteriostasis of tubercle bacilli *in vitro* in a shorter period than is now possible, to allow the detection of chemically unstable agents.

And, the necessity of selecting adequate criteria for evaluation of experimental chemotherapy in various forms of human tuberculosis is already well recognized by the clinician.

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## II. Enzymes in Tuberculosis

It is well known that various species, individuals in a species, and tissues within an individual vary in their response to the injection of living or dead tubercle bacilli. A consideration of certain tissue enzymes as possible factors in explaining these differences will be our second topic for discussion.

Because of the discovery that crude tubercle phosphatide, a phospholipid extract of the H37 tubercle bacillus, can alone produce typical tuberculous tissue with epithelioid cells, giant cells and caseation, the rôle of enzymes important in the breakdown of phospholipids has been investigated.

It was first shown (1) that a lecithinase acted to split off fatty acids and this reaction was followed by the action of phosphatase in further hydrolyzing the phosphatide to release free phosphoric acid. Then followed the discovery (2) that there were differences in the ability of lung and kidney extracts containing phospholipases from guinea pigs, rabbits and mice to break down tubercle phosphatide *in vitro*. The phospholipases from these sources yielded essentially comparable cleavage of lecithin as determined by the rate of appearance of free phosphorus. There were marked variations in their ability to split tubercle phosphatide, however. Mouse and rabbit preparations of lung and kidney caused strikingly better cleavage of tubercle phosphatide than did the enzymes from the guinea pig lung.

Many investigators (3, 4, 5) had observed that fatty acids, particularly unsaturated types, had the property of inhibiting tissue enzymes of various types—trypsin, cathepsin, liver esterase, pancreatic lipase and others. Therefore, attention was directed toward the fatty acids occurring in tubercle phosphatide. Oleic acid, an unsaturated acid of the principal variety found in the tubercle bacillus, and tuberculostearic acid, a saturated branched fatty acid obtained from the tubercle bacillus, were tested for lecithinase and phosphatase inhibition and observed to be active against lecithinase and particularly against the lecithinase of guinea pig lungs. Mouse lung enzymes, on the other hand, were resistant to the inhibiting effects of both oleic and tuberculostearic acids.

It is of particular interest at this point to mention that the guinea pig is more susceptible to infection with virulent human tubercle bacilli than the rabbit or the mouse and the incidence of tubercle formation in guinea pig kidneys is generally much lower than in guinea pig lungs. Thus, for the first time in the history of tuberculosis, one can correlate species and organ susceptibility with specific cellular enzyme activity.

The next step in this field of research was naturally an attempt to increase by some means or other the normal activity of phospholipases *in vivo* and thereby prevent the tissue destruction presumably due to the normal incapacity of tissues to break down the phospholipids of the tubercle bacillus.

It was known that the injection of crude tubercle phosphatide intraperitoneally in rabbits would result in the production of massive tuberculous tissues, as we have described. Therefore, a synthetic phosphatidic acid, cinnamoyl glycerol

phosphatidic acid, was injected intravenously into rabbits for a period before the intraperitoneal injection of tubercle phosphatide and continued for a prolonged period thereafter (6). This technique prevented the characteristic formations of tuberculous tissue in the peritonea and omenta of rabbits so treated, while the untreated controls showed the usual tissue reactions. Presumably, although not specifically proven, the synthetic phosphatidic acid so stimulated the phospholipase activity of the cells of the treated rabbits that the usual phospholipase inhibition by the fatty acids or other substances in the crude tubercle phosphatide was antagonized.

It must be mentioned that certain observers (7) have demonstrated that purified tubercle phosphatide, completely freed of bacillary debris and protein, did not produce tuberculous tissue. One is, therefore, forced to consider the possibility that the fatty acids present in pure tubercle phosphatide may not be the most important factors in the production of the tuberculous tissue. Experiments are now in progress to investigate whether or not Choucron's toxin has anti-phospholipase activity (see Part III, ref. 6), and the question naturally arises as to whether or not the good correlation between the differential phospholipase activity of various organs, the ability of extracts of those organs to retard or inhibit the multiplication of virulent tubercle bacilli (8) and the clinical incidence of progressive tuberculous lesions in those organs is a more or less accidental relationship. Nevertheless, the demonstration that cellular phospholipases are probably important factors in resistance to tuberculosis remains an important contribution to the understanding of tuberculous infections.

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### III. Some Advances in the Immunology of Tuberculosis and Postulation of a Specific Component of the Tubercle Bacillus Determining Virulence

The literature on the immunological aspects of tuberculosis began with the discovery of the tubercle bacillus in 1882 and has now become very voluminous. The arguments over the relation of allergy to tuberculin, on the one hand, and active immunity on the other, have frequently tended to be more metaphysical than scientific. Our discussion will, therefore, not be a review of the literature but a brief summary of certain fundamental observations on which most investigators are agreed and the postulation of a specific chemical component of tubercle bacilli determining virulence—the “P” factor.

Perhaps, it can safely be stated that, when any animal susceptible to infection with a particular acid-fast organism is injected with such bacilli after they have been killed by the shortest period of heating necessary to assure death of every organism in the culture used, that animal will show more or less resistance to subsequent infection with that organism. Also, every living acid-fast bacillary culture, which itself does not produce progressive disease in a particular animal species, will, when injected into that animal, produce more or less resistance to the subsequent injection of an acid-fast bacillary culture known to produce progressive disease in that species. Furthermore, too great trauma, in a chemical sense, will reduce the protection afforded in the first case, and in the second case the more closely related the two cultures are in a cultural and immunological sense, the more protection, in general, will be afforded (by “immunological” we mean here the classical relationships as demonstrated by bacillary agglutination, complement fixation, precipitin tests with the sera of “immunized” animals). Protection in most cases appears to be simply a prolongation of life of the animal, and it varies quantitatively from animal to animal, species to species, and with varying quantities of vaccination material and numbers of infecting organisms, as one would expect (1). Unlike other bacterial diseases in which “toxins” and factors such as we shall postulate for the tubercle bacillus are unimportant or absent and in which, therefore, the titre of serum antibodies to the complexes (somatic antigens) on the cell wall of the organisms correlates well with the measure of immunity to those diseases (2), there is no consistent correlation between tuberculin sensitivity (allergy) and immunity, on the one hand, or between agglutination, complement fixation, precipitins and immunity, on the other (3). The use of whole organisms, either living avirulent or killed virulent, has never produced results comparable to the protection which is afforded by the use of vaccination procedures with whole organisms in such a disease as typhoid in which it has been shown that immunization with two of the antigens on the cell wall is sufficient to afford marked protection (4). In this connection it should be mentioned that until recently no workers had been able to isolate from whole tubercle bacilli any antigen which when injected into animals produced immunity comparable to that produced by vaccination with whole cultures. However, Seibert (5) reported last year that she could produce sensitization to Old Tuberculin and develop gamma globulin “antibodies” which would agglutinate live

tubercle bacilli, inhibit their growth *in vitro*, and behave as specific precipitins for the fraction which she used as antigen. No definite protective effect against the subsequent injection of virulent tubercle bacilli has been reported for this special fraction, which was obtained by careful nontraumatic production of tuberculin in which there was a large component of high molecular weight protein. Also, Choucroun (6) has prepared an antigenic product with similar biological properties by extracting tubercle bacilli with paraffin oil, followed by extraction of the paraffin oil with various organic solvents. There are indications that this latter preparation will protect guinea pigs from infection with virulent tubercle bacilli, perhaps to a degree comparable with the protection afforded by methods using whole tubercle bacilli as others have described.

It is evident that the isolation of such a substance or substances from the whole organisms is an important advance in tuberculosis research. Such somatic antigens have, no doubt, an important part in protection against subsequent infection by producing antibodies (classical) to themselves as they lie exposed on the cell wall of the bacterial bodies, perhaps by limiting the spread and multiplication of the organisms in a two-fold manner: (1) by agglutination into clumps as can be demonstrated both *in vivo* and by sera *in vitro*; (2) by the prompt inflammatory, allergic reaction of the tissues after the manner of the mechanisms pictured by Menkin (7).

Purposely avoiding the very controversial problem of the relation of hypersensitivity to tuberculin to immunity (8, 9, 10), we turn to observations and considerations which, in our opinion, will lead to more fruitful future work in tuberculosis.

The studies of Woodruff and Kelley (11) have shown that, before classical immunological reactions can take place, avirulent tubercle bacilli, otherwise indistinguishable from virulent tubercle bacilli, do not have the capacity to multiply to any appreciable extent *in vivo*, whereas the virulent organisms do possess this characteristic property. This finding, we hope to demonstrate, should point the way for newly directed investigations of the tubercle bacillus with a final view toward isolating that chemical component of the virulent organisms which must in the final analysis yield a practical basis on which to allow a more fundamental knowledge of the pathogenesis of tuberculosis and, by increased understanding of the problems to be discussed shortly, a clearer approach to the pathological anatomy and physiology of the established disease.

Indeed, certain theoretical deductions of interest can already be derived from the published investigations of previous workers:

(1) Virulent and avirulent variants of certain strains of tubercle bacilli, although they betray their difference in their ability to produce progressive disease in experimental animals, on the chorio-allantoic membrane of the chick embryo, and, according to the experiments of Woodruff and Kelley, to multiply in the normal animal, do not differ consistently *in vitro* in their rate of growth, necessary growth factors or environmental conditions, although their antigenic structure has frequently been shown to have undetermined differences (12). We, therefore, postulate that virulent and avirulent cultures of tubercle bacilli differ in a

quantitative manner of population concentrations of organisms, possessing or not possessing the ability to synthesize that component which determines virulence (that is, the capacity for causing progressive tuberculosis by bacterial multiplication *in vivo*), and which, for convenience, we shall refer to as the "P" factor.

(2) No component of tissues has been demonstrated selectively to inhibit the multiplication of avirulent organisms *in vitro*, although the observations of Woodruff and Kelley indicate that such a substance or substances must be present *in vivo*—this bacteriostatic (or bactericidal) factor may be too unstable to demonstrate such activity during the long period that tubercle bacilli must be incubated to demonstrate a bacteriostatic agent. The observation of Lurie (13) that the monocytes of one of his resistant strains of normal rabbits were able to inhibit the multiplication of virulent organisms in the anterior chamber of the eye, whereas the monocytes of normal low-resistant strain rabbits were much less able to do this, certainly implicates the monocyte, at least, as a source of such a tissue component.

(3) The phagocytic cells of susceptible hosts are equally capable of phagocytizing virulent and avirulent tubercle bacilli. This places tubercle bacilli in a class distinct from those many bacteria of which the virulent species, as contrasted with the avirulent species, possess somatic antigens (capsular polysaccharides, etc.) which protect them from phagocytosis unless specific antibodies to those antigens are present to "opsonize" the bacterial bodies for phagocytosis. This is not meant to imply that tubercle bacilli do not possess specific somatic antigens or that circulating antibodies (or the possible "fixed tissue antibodies") may not hasten phagocytosis; but, this observation should direct attention again to what we consider the more important, fundamental, difference between virulent and avirulent tubercle bacilli: the distinctive ability of the former to multiply *in vivo*. Furthermore, we would emphasize the possibility that the postulated "P" factor may be a somatic antigen which only virulent tubercle bacilli are capable of elaborating under specific environmental conditions (most favorable in the tissues of susceptible hosts) and which may protect them either from phagocytosis or from the destructive effect of intracellular enzymes. The observations of Woodruff and Kelley (11) are significant in this respect. They noted that only after the third day subsequent to intraperitoneal inoculation of virulent tubercle bacilli in healthy guinea pigs did the organisms begin to grow freely in clumps, extracellularly as well as intracellularly. The slow growth of tubercle bacilli and the logarithmic character of the growth curve may explain this apparent lag phenomenon, but it is obvious that one must keep in mind the possibility that the organisms had to adapt themselves to the production of some protective substance which they did not produce in any great quantity during their previous growth *in vitro*.

It may be further postulated that different strains of tubercle bacilli, human, bovine, avian, etc., produce specifically different "P" factors to account for the differential susceptibility of various species of animals, but this is not essential, inasmuch as these strains of bacilli have cultural and biochemical characteristics

sufficiently different, perhaps, to account for this differential species susceptibility.

These considerations lead to the conclusion that for the past quarter of a century, at least, by far the majority of investigators in the field of immunology of tuberculosis have, in their concern for active immunity, overlooked a fundamental problem in tuberculosis—the investigation of the differences between virulent and avirulent organisms in a chemical as well as a biological sense in an attempt to identify the bacterial and tissue components which determine these differences. And, unfortunately, those who have sought such a bacterial component have used chemical methods which were not specifically adapted, it appears, for the isolation of many biologically important components of bacterial cultures (14). In the latter part of the last century and the early years of this century many attempts were made (15) to isolate a “poison” from virulent tubercle bacilli—all with questionable results probably because of the poorly developed chemical knowledge and techniques of the time. Choucroun (16), however, has recently isolated a very “toxic” substance with peculiar biological characteristics from virulent tubercle bacilli. In the course of her search for a “sensitizing” substance, she has isolated, by chance, an agent which in a dose of 2 gamma, injected intraperitoneally in paraffin oil, is usually lethal for the normal guinea pig. This substance is reported to be a polysaccharide ester of mycolic acid, perhaps one of the class of “Boivin antigens” (17, 18, 19) of importance in many bacteria as ectotoxins (?). There is some evidence, albeit questionable, that this carbohydrate-lipoid compound can be extracted in larger quantities from virulent than from avirulent tubercle bacilli. Whether or not it specifically contributes to the pathogenicity of virulent tubercle bacilli remains to be seen; it may or may not be the hypothetical “P” factor. There may well be a dissociation between the “P” factor and that factor or those factors which are associated with the clinical progress of the disease with its cachexia and the local pathological changes induced by the organisms. In other words, the “P” factor may be only a very specific antagonist of the normally present antibacterial tissue component, without any very generally toxic biological activity; and it may be different from that bacterial component postulated by Gerstl and others which inhibits tissue phospholipases and other enzymes (see Part II), thereby producing the characteristic caseation necrosis of tuberculous lesions. There are many observations by previous investigators which give clues as to where to look for “toxic” factors in the chemical fractionation of tubercle bacilli, including the following:

(1) The marasmic “filtrate disease” of Pinner and Voldrich (20), caused by bacteria-free culture filtrates of virulent tubercle bacilli, unfortunately given insufficient attention.

(2) The antilecithinase factor of Calmette in fresh bacillary cultures and tuberculin prepared in the cold (21).

(3) The polysaccharide preparations of Kropp *et al.* (22) which include a potent, protective antigen, a carbohydrate-lipid complex (23).

It must be obvious that only by careful atraumatic chemical fractionation of cultures and culture filtrates of tubercle bacilli, grown under many different con-

ditions in an effort to afford maximal production of the postulated "P" factor, and the development of adequate biological tests, can our knowledge and understanding of tuberculosis be advanced. Fortuitous steps in the chemotherapy of tuberculosis should not discourage investigation of means to prevent and, possibly, to treat tuberculosis by isolation of the factor determining virulence and of other components of tubercle bacilli having significant effects upon the local and general metabolic processes of the host.

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### SUMMARY AND CONCLUSIONS

In this paper we have attempted:

- (1) To summarize our knowledge of the chemotherapy of tuberculosis with sulfonamide-like agents.
- (2) To evaluate the possibilities of chemotherapy in the future.
- (3) To review the important advances in our understanding of biochemical factors in the local pathology of tuberculous lesions.
- (4) To discuss the present state of our knowledge of the immunology of tuberculosis.
- (5) And to postulate the existence of a specific chemical component of tubercle bacilli which determines their virulence.

In conclusion, we venture to predict that in man's war against the *Wehrmacht* of the "little red devil" an understanding of the biochemistry of the disease—the elucidation of the specific components of the organisms which interfere with normal metabolic processes—the tissue components which tend to inhibit the multiplication of the bacteria and to destroy or antagonize the effects of their products—and an ounce of prophylactic "antibodies" (not necessarily in the classical sense) will be worth a pound of chemotherapeutic agents.

#### SUMARIO Y CONCLUSIONES

En este trabajo se ha tratado de:

(1) Sumarizar nuestros conocimientos acerca de la quimioterapia de la tuberculosis con los sulfonamidos.

(2) Justipreciar las posibilidades de la quimioterapia en el futuro.

(3) Repasar los más importantes adelantos en nuestra comprensión de los factores bioquímicos que intervienen en la patología local de las lesiones tuberculosas.

(4) Discutir el estado actual de nuestros conocimientos de la inmunología de la tuberculosis.

(5) Y postular la existencia de un componente químico específico de los bacilos tuberculosos que determina la virulencia de los mismos.

Al concluir, aventúrase la predicción de que en la guerra humana contra el *Wehrmacht* del "diablillo rojo", la comprensión de la bioquímica de la enfermedad—la dilucidación de los componentes específicos de los microbios que intervienen con los procesos metabólicos normales—los componentes histológicos que tienden a inhibir la multiplicación de las bacterias y a destruir o antagonizar los efectos de sus productos—y que una onza de "anticuerpos" (no necesariamente en el sentido clásico) servirá de más que una libra de agentes quimioterapéuticos.



## PROMIN IN EXPERIMENTAL TUBERCULOSIS

Effects of Prolonged Treatment with Sodium P,P'-Diaminodiphenylsulfone-N,N'-Diox-  
trose Sulfonate (Promin) on Subsequent Reinfection

WILLIAM H. FELDMAN<sup>1</sup> AND H. CORWIN HINSHAW<sup>2</sup>

It has been shown repeatedly that the course of tuberculosis in guinea pigs can be strikingly modified as a consequence of certain antituberculosis substances (1 to 8). Of much significance is the fact that desirable results occur even though the beginning of treatment is delayed until well developed lesions are present in the inoculated animals. When infected guinea pigs are treated daily for a period of six months, there is a large percentage of the treated animals in which parenchymal lesions cannot be found or in which the lesions are of minimal size and all show signs of healing or retrograde changes. However, virulent tubercle bacilli persist in the tissues in a large percentage of "successfully" treated guinea pigs. This can be demonstrated by inoculating normal appearing spleens of treated guinea pigs into normal recipients (1, 9).

This raises a pertinent question. If the parenchymal tissues of treated guinea pigs contain tubercle bacilli capable of producing progressive lesions in normal recipients, why are the organisms unable to exert a progressive pathogenicity in the animals that are being treated? The obvious explanation would be the specific deterrent effect exerted either directly or indirectly by the therapeutic agent.

In a previous report (1) an experiment was described which sought to determine whether the latent infection would promptly become reactivated when the medication was discontinued. In the experiment referred to, guinea pigs were deprived of therapy for eighty-four days after a course of treatment of like duration. This period has been adequate to cause the death of all animals in the untreated control group. It was found that some of the animals that had been treated and subsequently deprived of therapy had no visible lesions when killed for necropsy but that virulent tubercle bacilli were demonstrable in the spleens. This led to the tentative opinion that some factor of acquired immunity was operating to suppress the activity of the tubercle bacilli even after the chemotherapeutic influence was withdrawn. If this hypothesis be correct, it should be possible to demonstrate in such animals an increased resistance to reinfection when compared with similar animals that had not previously experienced infection with tubercle bacilli. It would also be of interest to know how long this presumed resistance—if present—continues against endogenous or exogenous reinfections. Medlar and Sasano (5) have contributed significantly to this problem, although they did not report experiments in which reinfection was done.

In order to ascertain whether apparent "recovery" from a progressive tuberculous infection in the guinea pig stimulates sufficient resistance or immunity to prevent the activation of latent residual infection or to protect the animal against

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an exogenous reinfecting dose of tubercle bacilli, the following experiments were done.

# FIRST EXPERIMENT

*Method:* Each of a group of 48 guinea pigs was inoculated subcutaneously with 0.0005 mg. of a seventeen day old culture of human tubercle bacilli, H37RV. Starting six weeks later, 19 of the animals were medicated daily with promin.<sup>3</sup> Promin was added to the feed to the amount of 1 per cent by weight.<sup>4</sup> Medication was continued for 365 days. Twenty-eight days after treatment was discontinued, the 13 surviving animals in the group of 19

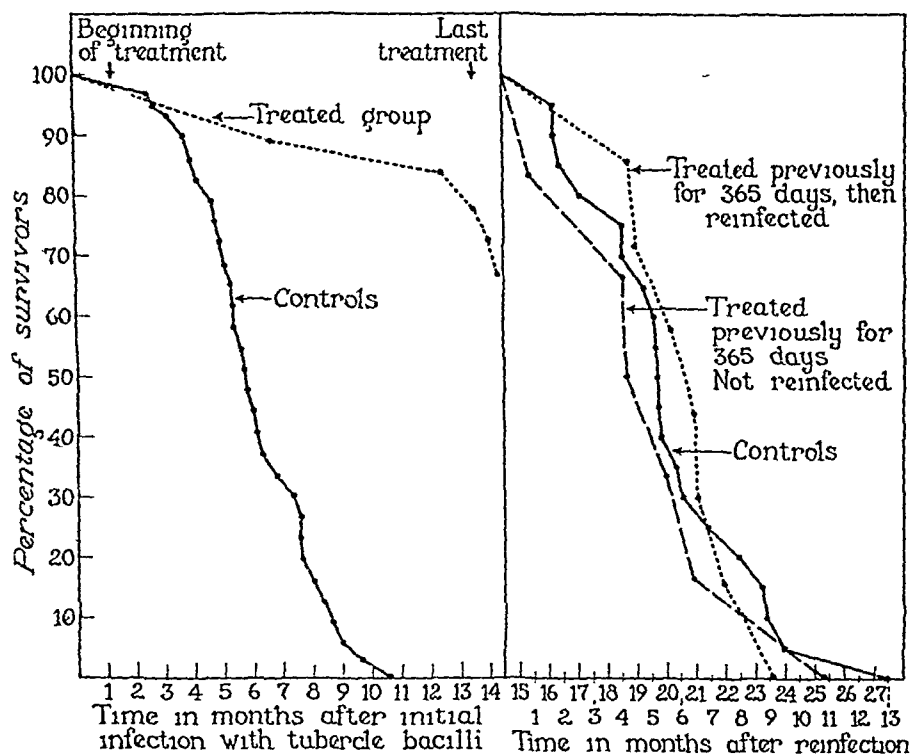


CHART 1. Survival of tuberculous guinea pigs treated with promin and of untreated controls in first experiment

animals that had been treated were divided into two groups containing 6 and 7 guinea pigs, respectively. The group containing 7 guinea pigs was again inoculated with 0.0005 mg. of an eighteen day old culture of the same strain of tubercle bacilli used in the initial inoculations and in addition another group of controls consisting of 20 guinea pigs was also inoculated. None of the animals received further treatment and the experiment was continued until all of the animals had died.

<sup>3</sup> Sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate. This drug was supplied through the courtesy of Dr. E. A. Sharp and Dr. L. A. Sweet, Parke, Davis & Company, Detroit, Michigan.

<sup>4</sup> The average daily intake of the drug per animal was estimated to be 400 mg.

*Results:* The differences in the survival time of the respective groups of guinea pigs are shown graphically in chart 1. The last animal in the first group of controls died 318 days after inoculation. During this period only 2 of the 19 animals that were being treated died. Before the group that had been treated was divided for the second phase of the study (435 days after inoculation with tubercle bacilli) a total of 6 guinea pigs had died. This represents 32 per cent of the group that had been medicated. It is evident that treatment had interfered with the natural course of the infection since the last of the controls had died 117 days prior to the time the second phase of the experiment was started.

TABLE 1  
Data on first experiment\*

GROUP	ANI- MALS	SURVIVORS DURING PERIOD OF TREATMENT, PER CENT	SURVIVAL TIMES		AMOUNT OF TUBER- CULOSIS EXPRESSED NUMERICALLY (MAX. 100)
			Average, days	Extremes, days	
Controls.....	29	0	(29) 184	74-318	92
Treated.....	19	68	(6) 318†	87-428	(6) 49
Controls.....	20	—	171	53-391	86
Previously treated; not re- infected.....	6	—	593 186 ‡	460-760	77.3
Previously treated; rein- fected....	7	—	624 217 ‡ 189§	565-707	52.8

\* The data in the two spaces immediately above the double line pertain to the guinea pigs that were utilized in the first, or therapeutic, phase of the study. Forty-eight animals were inoculated with tubercle bacilli. Starting forty-two days later, 19 of them received promin for 365 days; 6 died during the period of treatment or within twenty-eight days after it. The 13 guinea pigs that survived therapy were used in the second phase of the study. The subsequent results were compared with the results obtained from 20 untreated controls.

† Average for the 6 animals that died during period of treatment or within twenty-eight days after it.

‡ Average survival time after treatment was discontinued.

§ Average longevity after reinfection.

The second phase of the study began when approximately half of the previously treated animals were reinfected with tubercle bacilli. When the longevity of the reinfected group is compared with that of the group that was not reinfected and with that of the second group of controls, no significant differences are recognizable. It is evident that previous infection and treatment did not provide increased resistance sufficient to extend the longevity of the reinfected animals.

The data pertaining to longevity and to the amount of tuberculosis expressed numerically are given in table 1. While it appears to be true that the animals that had been treated previously had somewhat less tuberculosis than the control group, the differences are of only moderate degree and are not impressive.

## SECOND EXPERIMENT

*Method:* Each of a series of guinea pigs was inoculated with 0.0005 mg. of a twenty-three day old culture of tubercle bacilli, strain H37RV. Six weeks later the animals were divided into two groups. One group of 28 animals was designated untreated controls and the other group of 56 animals was treated orally with promin.<sup>5</sup> Treatment was continued for 210 days and after a lapse of twenty-eight days the survivors in the group that was treated were divided into two groups containing 18 and 17 guinea pigs, respectively. The group containing 17 animals was then reinoculated with 0.0005 mg. of an eighteen day old

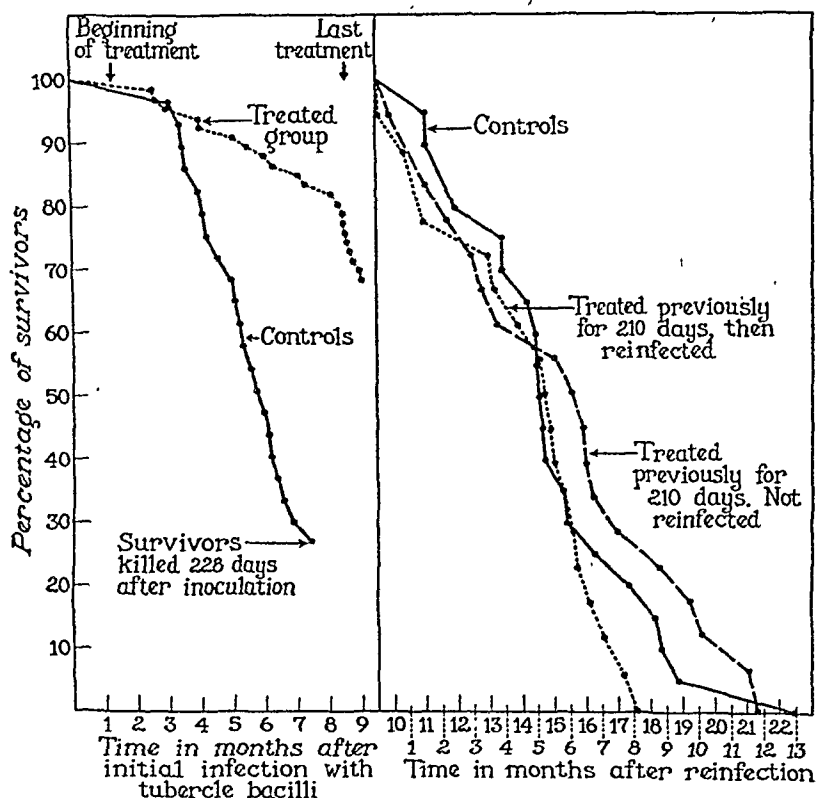


CHART 2. Survival of tuberculous guinea pigs treated with promin and of untreated controls in second experiment

culture of the same strain of tubercle bacilli used to make the initial inoculation.<sup>6</sup> At the same time each of 20 additional guinea pigs, not previously infected, was similarly inoculated. These constituted the controls for the second or reinfection phase of the experiment.<sup>7</sup> The experiment continued until all of the animals in the second phase of the study had died.

<sup>5</sup> The procedure of medication, dosage and so forth were the same as described in the first experiment.

<sup>6</sup> The animals were inoculated with portions of the same bacterial suspension used to reinfect the previously treated guinea pigs in experiment 1.

<sup>7</sup> This group also served as controls for the first experiment, since the second or reinfection phase of both experiments was conducted concurrently.

*Results:* The differences in the survival times of the respective groups of animals in the first and in the second phases of the study are recorded graphically in chart 2. It will be noted that in the first phase of the experiment there was a significant difference between the mortality of the animals that were treated and the mortality of those that were not. During the period of medication 13 (23 per cent) of the treated animals had died. However, 8 additional animals in the group that had been treated died before the second or reinfective phase of the experiment was started.

TABLE 2  
*Data on second experiment\**

GROUP	ANI- MALS	SURVIVORS DURING PERIOD OF TREATMENT, PER CENT	SURVIVAL TIMES		AMOUNT OF TUBER- CULOSIS EXPRESSED NUMERICALLY (Max. 100)
			Average, days	Extremes, days	
Controls.....	28	28.5	(20) 153†	92-210	84.1
Treated.....	56	62.5	(21) 219‡	78-273	16.8
Controls.....	20	—	171	53-391	86
Previously treated; not re- infected.....	18	—	465 213§	306-640	80
Previously treated; rein- fected.....	17	—	452 200§ 172	294-528	86

\* The data in the two spaces immediately above the double line pertain to the guinea pigs that were utilized in the first, or therapeutic, phase of the study. Eighty-four guinea pigs were inoculated with tubercle bacilli. Starting forty-two days later, 56 animals received promin for 210 days; 21 died during the period of treatment or within twenty-eight days after it. The 35 animals that survived therapy were used in the second phase of the study. The subsequent results were compared with the results obtained in 20 untreated controls. (The controls in this instance were the same as were used in the first experiment.)

† Eight animals in poor condition were killed 228 days after infection. The average survival time for the group (28) was then 173 days.

‡ Average longevity of the 21 animals that died during period of treatment or within twenty-eight days after it.

§ Average survival time after treatment was discontinued.

|| Average longevity after reinfection.

In the reinfective phase of the study both groups that had been treated previously had an average longevity slightly greater than that of the controls but, as was true in experiment I, there was no striking or significant difference in the average longevity of the three groups.

That no effective resistance had developed as a consequence of treatment following the initial inoculation was clearly evident in the amount of tuberculosis present in the animals comprising the three groups utilized in the second or reinfective phase of the study. The indices of infection expressed numerically for the respective groups are given in table 2. That treatment had a favorable influence on the course of the infection was evident by the results of the first

phase of the experiment. Not only was there a lower rate of mortality among the animals that received promin than among the controls but also the amount of disease in the treated animals that died averaged 16.8 compared with 84.1 for the untreated controls.

#### COMMENT

One might properly assume that, when a guinea pig is inoculated with a small dose of virulent tubercle bacilli which are permitted to multiply and disseminate for several weeks before being exposed to the effects of a therapeutic agent, immunogenic processes would be stimulated to at least some degree. When the natural resistance—which in guinea pigs must be of a low order of potency—is assisted by the action of an effective therapeutic substance to the extent that a progressive destructive disease is converted to one that is nonprogressive and which may even resolve, fibrose or calcify, it would appear that the situation is analogous to that resulting from vaccination. If this were true, there should be a measurable enhancement of the resistance following reinfection.

Our data indicate definitely that under the conditions of the two experiments described a significant modification of the disease following reinfection did not occur. Furthermore, our results were in general agreement with those of Medlar and Sasano (5) in that prolonged treatment with promin, although extending the life of the infected animal for many months beyond that of the untreated controls, did not prevent, after treatment was discontinued, the activation of the infective process and subsequent death from tuberculosis. It should also be noted that the ability of promin to suppress tuberculosis was retained for prolonged periods and apparently was not reduced by development of "drug fastness" by the organisms under the conditions imposed by these experiments.

Tuberculosis may remain latent in the human body for long periods, the organisms residing in lesions similar to the latent lesions noted in the guinea pigs of these experiments. In the case of human beings the organisms are held in abeyance by natural and acquired factors of resistance rather than by a bacteriostatic drug. Malaria is a disease to which man has little natural resistance and the use of "suppressive treatment" is widely practiced, quinine or atabrine being utilized in doses adequate to prevent progress of the disease but not adequate to destroy the parasites. In such cases clinical malaria frequently develops when treatment is discontinued. The fact that an antimalarial drug or an antituberculosis drug serves only a suppressive function does not speak against its practical therapeutic efficacy. Nevertheless, the ideal drug in either instance would be one capable of permanently eradicating all infection. The development of such a chemical compound does not appear impossible when one recalls other chemotherapeutic triumphs.

#### SUMMARY AND CONCLUSIONS

Two experiments were conducted to determine what effect, on subsequent reinfection, prolonged treatment of tuberculous guinea pigs with sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate (promin) might have. In both experiments the disease was induced by human tubercle bacilli, strain

H37RV, and had been established for forty-two days before treatment was started. Treatment was continued in the two experiments for 365 days and 210 days, respectively. After an interval of twenty-eight days approximately one-half of the animals that had survived the period of medication were reinfected with the same strain of tubercle bacilli used to produce the infection originally. For comparison, untreated controls were included in both the first and second phases of the experiments. The second or reinfection phase of the experiments was continued until all of the animals had died. The results indicate definitely that:

1. Guinea pigs infected with tubercle bacilli and treated continually for a prolonged period with promin will, after medication is stopped, eventually die of tuberculosis.

2. Previous prolonged treatment with promin followed by superinfection had no significant effect on the consequent course of the disease.

3. No evidence was obtained to suggest development of "drug fastness" by this strain of tubercle bacilli to the chemotherapeutic effects of promin under the conditions of this experiment.

#### SUMARIO Y CONCLUSIONES

Los dos experimentos descritos tenían por propósito determinar qué efecto puede ejercer sobre la reinfección subsiguiente el tratamiento prolongado de los cobayos tuberculosos con sulfonato de bidextrosa N,N' diaminodifenilsulfona p,p' sódico (promina). En ambos experimentos se provocó la enfermedad con bacilos tuberculosos humanos, cepa H37RV, y antes de iniciar el tratamiento había estado establecida por espacio de 42 días. En los dos experimentos el tratamiento continuó por 365 y 210 días, respectivamente. Tras un plazo aproximado de 28 días se infectó aproximadamente la mitad de los animales que habían sobrevivido el período de medicación con la misma cepa tuberculosa utilizada para producir la infección primitivamente. Para fines de comparación, tanto en la primera como en la segunda fase de los experimentos, figuraron testigos no tratados. La segunda fase, o sea la de reinfección de los experimentos, continuó hasta morir todos los animales. Los resultados indican definitivamente:

1. Los cobayos infectados con bacilos tuberculosos y tratados continuamente durante un período prolongado con promina, murieron tarde o temprano de tuberculosis, después de suspenderse la medicación.

2. La prominoterapia prolongada previa seguida de superinfección no ejerció efecto significativo sobre la evolución subsiguiente de la dolencia.

3. No se obtuvieron datos indicativos de desarrollo de "farmacorresistencia" de parte de esta cepa del bacilo tuberculoso a los efectos quimioterápicos de la promina en las condiciones de este experimento.

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# TYPES OF TUBERCLE BACILLI IN BIRDS AND MAMMALS<sup>1</sup>

Their Incidence, Isolation and Identification

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Although tuberculosis is wide-spread throughout the animal kingdom, there are only three significant types of bacilli—the human, the bovine and the avian—responsible for the disease in warm-blooded animals. Of the three types, the majority originate from human sources and are of the human variety. Bovine infections, while not so numerous, occur both in animals and man to such an extent that they constitute a genuine health hazard. The avian bacillus, indigenous in the *Gallinaceae* and found in other species of fowl as well as in many animal species, is a rarity in human beings. It plays an important rôle, however, in animal industry and causes confusion in the diagnosis of the other two types.

The extent to which tuberculosis exists throughout the animal kingdom is still imperfectly understood. According to Loewenstein (1) every animal "from the elephant to the shrew . . ." may be infected by at least one type of tubercle bacillus. Calmette (2) as well as Griffith (3) restrict the conditions of infection to the domestic state and assert that no animal in its native haunts ever develops tuberculosis. Bushnell (4) has shown that man away from civilization is also relatively free from tuberculosis.

While it is generally agreed that animals away from all contact with civilized man and his domesticated animals rarely, if ever, become tuberculous, there are certain instances of proved spontaneous tuberculosis in the wild state, albeit in animals in varying proximity of domestic animals.

The infection of voles (5) by the Wells bacillus is perhaps the best example. Mitchell and Duthie (6), as well as others, found tuberculosis in wild crows; Van Es and Schalk (7) have reported the disease in sparrows, and Magnusson (8) found tuberculosis in a deer that frequented the locality of a chicken farm. Ground squirrels were found by McCoy (9) to be infected with bovine bacilli. Feldman (10) cites trustworthy reports of the presence of spontaneous tuberculosis in wild rabbits frequenting the neighborhood of infected animals.

It seems axiomatic, therefore, that tuberculosis in animals, like the disease in man, cannot exist without direct or indirect contact. Furthermore, the prevalence of the disease in any individual or group is proportionate to the closeness of the contact.

Irrespective of the problem of contact and domesticity, however, the fact is that a vast number of animal species have been found to be susceptible while others are resistant to one or more types of tubercle bacilli.

The peculiar relationship of tuberculosis to domestic or captive animals, as well as its probable appearance in the late phase of man's development, raises the

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question of time and place of origin of the disease. Although tuberculosis as a plague is well within the historic era, the finding of tuberculosis in preserved bones of certain ancient peoples indicates the presence of the disease before the dawn of history. It is probable that the rise of the disease is related to the increase in contact, as families formed tribes and tribes settled in villages and cities. Perhaps at about the time that man changed from a solitary to a socialized existence, tuberculosis became an established disease. It would also be logical to suppose that, as man became more gregarious, there occurred a collateral increase in the herding of man's domestic animals and a corresponding increase in animal tuberculosis.

Most of the studies on tuberculosis in animals have dealt with susceptibility and the incidence of infection. Some have reported the types of bacilli found. A few studies, including the meticulous work of Nieberle (87) for common domestic animals and monkeys, Feldman's (10) work on avian bacillus infections, and a few others, have emphasized pathology and pathogenesis. Immunological phenomena have been studied only in laboratory animals and cattle, but, in general, little is known in other animal species.

As a rule, therefore, the work on all but a few common animal species is too meagre to make comparisons except of the susceptibility, incidence of infection and types of bacilli usually found. Accordingly our brief review of the subject will generally be confined to one or more of these phases of the problem.

Next to man, cattle have been the most common locus of tubercle bacilli. According to Haupt (11) the incidence of tuberculosis in cattle in German abattoirs from 1904 to 1924 was 18.98 per cent, as compared with swine with 2.10 per cent; sheep, 0.16 per cent; goats, 0.85 per cent; and horses, 0.14 per cent. As a result of the high virulence of the bovine type for human beings, the bovine bacillus in the days of the Koch era has been reported to have caused as high as 10 per cent of all human tuberculosis, appearing commonly as lymphatic, bone, serous membrane, as well as pulmonary lesions. The inspection of herds and pasteurization of milk in some countries have mitigated, if not largely eradicated bovine infection; but the work of Griffith (12) in England and Blacklock (13) in Scotland bears witness that it is still prevalent in their respective countries, commensurate with their lack of progress in the methods of control of the disease in animals. Bovine types of infection in human beings also seem to be still prevalent in other countries, for example Argentina (14). On the other hand, human strains do not play any significant rôle in cattle infections, as proved by the fact that Feldman (15) was able to find only 9 proved cases and reported one of his own. The avian bacilli are intermediary in position between human and bovine in the effects on cattle. Van Es (16) and Van Es and Martin (17) found that almost 10 per cent of certain benign infections in cattle are caused by avian bacilli.

Closely resembling the bovine type of disease in cattle is the bovine infection in the rabbit. The reaction in the rabbit, observed by Villemin (18) many years before the discovery of the tubercle bacillus, has since been used for typing the bovine strains in the laboratory. Avian infection in rabbits is slightly less severe

than the bovine and is of a septicemic type (Yersin). The human bacillus is much less virulent for the rabbit than either of the other two strains.

The type of disease in the goat is rather anomalous, since the adult animal is much more resistant and the young less resistant than are those of the corresponding ages in cattle. Otherwise, goats seem to react similar to cattle. The incidence of goat infections in France and Germany, according to Calmette (19), ranges from 0.17 to 0.77 per cent, but in America and England tuberculosis in goats is extremely rare. For example, the United States Bureau of Animal Industry was only able to find one case in 317,000 slaughtered animals.

The sheep possesses much resistance to all strains of tubercle bacilli, but is occasionally infected with the avian bacillus, as first shown by Griffith (20). Harshfield, Roderick and Hawn (21) in North Dakota found 25 out of 26 cases of tuberculosis in sheep to be of the avian type. Others have found similar results.

For unexplained reasons, the hog is one of the most susceptible of all animals to the bovine and avian bacilli and also is susceptible to the human type. Eastwood and Griffith (22) found about 60 per cent bovine, 30 per cent avian, 1 per cent human and a residual percentage of atypical strains in 78 cultures from 100 tuberculous swine. The British Commission (23) found in 59 cultures from swine that 50 were bovine, 5 avian, 3 human and one mixed avian and bovine. Van Es and Martin (24), however, in Nebraska where bovine tuberculosis is rather well controlled, found 88.51 per cent avian, 6.22 mixed and 5.21 mammalian tubercle bacilli. The extent to which human type tubercle bacilli exist in hogs is not well established, but Feldman (25) found 75 tuberculous hogs out of 264, which were fed unheated garbage. From these infected animals he isolated 47 cultures of tubercle bacilli, of which 35 were avian and 12 human. The infections were chiefly confined to the cervical and mesenteric lymph nodes. The hog, therefore, seems to be rather easily infected with the human strain and is unique in that it is one of the few animals capable of being infected with and disseminating all three types of tubercle bacilli.

The horse, and especially the ass, are of the least susceptible of common domestic animals to all types of tubercle bacilli. Nevertheless, Calmette (26) and Griffith of the British Commission (27) report that the horse is easily infected experimentally with the avian strain. Feldman (28) affirms that most spontaneous infections in the horse are, as in the sheep, due to avian bacilli.

There is a wide variation of response to tuberculous infection in rodents and small burrowing mammals. The guinea pig, one of the most susceptible of all animals to the bovine and human strains, is little affected by the avian type. The opposite is true of the laboratory rat, and especially of mice, which may be infected with the avian strain but are more resistant to the bovine and human strains. The cotton rat and hamster (a spermophile), however, are susceptible to bovine and human types. Feldman (29) was able to infect a series of striped gophers with all three types of tubercle bacilli but the bovine and human were more virulent than the avian. Curiously, Brooke's (30) work on the vole reveals that it is more susceptible to the bovine strain than to the so-called "vole" strain itself.

Dogs are susceptible to both bovine and human types, but more resistant to both than is man. Avian infections are rare in dogs. Feldman (31) was able to find only one report of spontaneous avian tuberculosis in dogs. The same author (32) reports that even inoculation of large doses of avian bacilli in dogs produces only a mild disease at the most, with many inoculations producing no effect at all. Although experimental inoculations of the bovine bacillus are slightly more virulent in dogs than the human, Calmette (33) states that they are more frequently infected by the human strain, presumably because of exposure to tuberculous masters. It should be pointed out also that in most countries the opportunities for bovine infections are decreasing more rapidly than for human infections. The incidence of tuberculosis in dogs, however, varies greatly in different localities. Douville (34) in a representative series reported about 4 per cent in 20,000 autopsied dogs in Paris.

Felines, represented by the house cat, are generally reported to have less tuberculosis than canines. Dobson (35) reported from Edinburgh 11 cases (2.2 per cent) in 264 autopsied cats, all of the bovine type. Hjärre (36) in Stockholm reported his findings of tuberculosis in dogs and cats from 1908 to 1937. For dogs the results for the three decades were 1.8 per cent of 434, 2.1 per cent of 270 and 5.4 per cent of 2,509 cases, respectively. About 70 per cent of 74 cases typed were of the human variety. In a much smaller number of cats the same author found 0, 2.0 and 4.8 per cent in the same time intervals, respectively. Only one out of 7 cultures recovered from cats was of the human type. The other 6 were bovine. Most authors have failed to find the human type in cats at all. Lovell and White (37), however, reported 4 human strains out of 56 cultures from cats. Chaussé (38), on the other hand, was unable to produce disease even by feeding cats with the human type bacillus mixed in their food. No reports are available on avian tuberculosis in cats.

As to the general incidence of tuberculosis in cats, Douville (39) reported 1 per cent at the same time he found 4 per cent in dogs in the city of Paris. It seems clear that tuberculosis in cats may be expected to fluctuate with the incidence of bovine tuberculosis and that the disease in dogs will parallel the sum total of all mammalian tuberculosis.

Among the higher mammals, the primates below man are susceptible to both the human and bovine type of infection, with the avian type playing a negligible rôle, as in man. Nocard (40) and others state that monkeys are slightly more susceptible to bovine than human tubercle bacilli. The work of Rabinowitsch (41), Fox (43), Nieberle (88) and many others has contributed much to our knowledge of tuberculosis in primates. Fox states that old-world monkeys (*Simiadae* and *Cercopithecadae*) are more susceptible to tuberculosis than are new-world monkeys (*Cebidae*). The more distantly related lemurs (*Lemuridae*) were found to have about half the tuberculosis incidence of the common primates. In 32 specimens of marmosets (*Hapalidae*) he found no tuberculosis at all. From our own limited observations of tuberculosis in common primates the orang (*Simia satyrus*) seems to develop the most progressive type of disease. It resembles the type found in the human infant. The macaques (mostly *Rhesus*)

and green monkeys (a few species of *Cercopithecus*) revealed slightly more resistance than the oranges while the gorilla (*Gorilla gorilla*) and, more particularly, a few species of new-world monkeys (*Cebidae*) showed either a more chronic form of tuberculosis or a more atypical localization of the infection.

Detailed knowledge is still lacking, however, in all but a few common species of primates especially with regard to immunology, pathology and pathogenesis. In general, according to Nieberle and Fox, the tubercle in primates consists of more caseation and less cellular reaction than in human tuberculosis. The variations in incidence and type of bacillus are probably due more to environmental factors (such as popularity with human visitors) than to any peculiarity of the animal species.

Barnyard chickens are susceptible and, in fact, contract avian tuberculosis as a specific disease. All closely related species, domestic and wild; are also susceptible to the avian type of infection. Practically all fowl have been reported to contract the avian type of tuberculosis, but some, like ducks and geese, reveal much resistance to it.

On the other hand, avian infections, as stated before, are exceedingly rare in human beings.<sup>3</sup> A possible source of danger to man, however, may arise from certain bird pets, not because of the avian bacillus but because they may be carriers of mammalian bacilli. Parrots and parrakeets have been reported by Cadiot, Gilbert and Roger (44) to be susceptible to spontaneous infection by all three types of tubercle bacilli. Together with swine they are apparently the only creatures known at present to act as vectors for the three types of tubercle bacilli of warm-blooded animals. From our present meagre knowledge, the susceptibility of other birds to tubercle bacilli seems to be as variable as that of mammals.

As a result of the preceding cursory review, it may be observed that warm-blooded animals exhibit all degrees of susceptibility to the three principal types of tubercle bacilli, ranging from an extensive disease to rare and benign infections. However, it is apparent that there are great gaps in our knowledge concerning animal tuberculosis and that there is no rule by which the disease in any given species can be known, except by accurate study and experiment.

The problem of animal tuberculosis is, therefore, quite involved, poorly understood and touches on numerous activities of life. There are aspects chiefly of interest to bacteriologists, others of vital concern in animal husbandry, while still others concern food industry and public health. Examples of the latter are the transmission of the disease from man to certain animals, transmission from one animal to another, and transmission of the disease from animals to human beings. In view of the facts mentioned, therefore, it seemed opportune to suggest a simplified technique of typing tubercle bacilli which may serve as a preliminary method in any circumstances but which would be especially suitable for small laboratories where facilities are limited.

The greatest drawback thus far in dealing with animal tuberculosis has always

<sup>3</sup> The subject of avian tuberculosis has been admirably and completely treated in *Avian Tuberculous Infections* by William H. Feldman, 1938, Williams & Wilkins, Baltimore.

been the uncertainty of recovering strains of bovine bacilli. Culture methods have gradually overcome this difficulty since growth of bovine bacilli may now be obtained almost as readily as that of human bacilli. In the last analysis the typing resolves itself into a refined study of pathogenicity in the test animals and the variations of growth on certain types of culture media.

Villemin (45) was the first worker to observe a difference in pathogenicity of tubercle bacilli in finding that human sputum did not kill rabbits as quickly as tuberculous pus from cattle. Rivolta (46) in 1889, Maffucci (47) in 1890-1892, and Straus and Gamaleia (48) in 1891 were the first to isolate the avian type and to characterize it as distinct from the mammalian. This work was followed in 1896 by Theobald Smith's (49) classical identification of the bovine type. However, it was not until 1901 that Koch (50) proclaimed in London at the International Tuberculosis Congress the existence of the bovine type—not because of cultural differences which had been demonstrated by Smith (49) but because of the differences in pathogenicity of the two strains. On the one hand, the human type of infection in man is chiefly confined to the lungs, whereas if the infection is bovine in type it usually affects the bowel first. On the other hand, is the fact that human bacilli produce only local lesions in the calf similar to those which Villemin (45) found in the rabbit.

Park and Krumwiede's (51) use of the rabbit for differentiation in 1910 marked a great advance in the separation of human and bovine types. By using a large dose (1.0 mg. or more) and a small dose (0.01) the two types were easily separated. The bovine type, when injected intravenously in the small dosage, was found to kill rabbits with a generalized disease within three to five weeks, while the human type even in the large dosage produced no more than a chronic disease, which after two months consisted at the most only of scattered tubercles in the lung, kidneys or both. Griffith (52) has shown that large dosage of human bacilli sometimes produces extensive disease and that the differences between bovine and human infections in the rabbit are sharpest in dosage of 0.01 to .001 mg. Since Oehlecker's (53) work, the 0.01 mg. intravenous dosage is usually employed. Other animals, notably the calf, have been recommended as test animals, but use of the larger animals has been too expensive or otherwise impractical.

The guinea pig's marked resistance to the avian type, as shown by Bretey and Laporte (54), make it an ideal test animal, and it has been highly recommended by Feldman (55) for identifying avian strains. There are very few instances where avian bacilli have been found to infect the guinea pig. Griffith (56) reported spontaneous infection in 2 cases, and Van Es and Martin (57) reported a guinea pig with marked susceptibility to avian bacilli. Rossi (58) reported an unusually virulent avian strain for guinea pigs. These exceptions, however, are so rare that they do not interfere with the use of guinea pigs as a test animal for ruling out avian strains. When a strain is obtained from chickens, or when it is found to cause tuberculosis in chickens, the type is obvious because, so far as is known at present, only avian strains kill chickens in small dosage. Inasmuch as chickens are not always convenient for use in small laboratories, the introduction of the guinea pig as a test animal is timely. A rather large dosage (0.1 to 1.0 mg.)

of avian bacilli generally produces in the guinea pig no more than a rapidly healing local lesion, whereas the other types are virulent, with the exception of degenerated strains, such as are sometimes found in lupus.

In the determination of cultural characteristics of the three principal strains of tubercle bacilli, progress has extended over a period of about fifty years. Since the present study concerns largely the cultural differentiation of human from bovine strains, the emphasis will be placed upon the isolation and identification of these two strains rather than upon a general discussion of the subject of culturing all the variations of *Mycobacterium tuberculosis*.

Theobald Smith's success in isolating the bovine type was of great importance and was achieved by using Koch's coagulated cow serum. On this medium, Smith was able to grow bovine strains which failed to grow on Nocard and Roux's (59) glycerinated agar medium. Dorset (60) used coagulated egg to which Lubenau (61) later added glycerin. In his early work, Griffith (62) used egg to isolate cultures and glycerinated potato to separate bovine from human strains, but later (62) he used exclusively glycerinated and non-glycerinated egg. Kirchner (63) and Laporte (64) used equal parts of egg-yolk and beef serum. Capaldi (65) first used egg-yolk and agar, a medium recently improved by Herrold (66) and Feldman (67). Pawlowsky (68) first used glycerinated potato, but it has since been improved by Calmette (69) and Corper (70). Calmette added bile which was supposed to be specific—the ox bile for bovine bacilli and human bile for human bacilli. Liquid media in the form of glycerinated bouillon was used by Kossel, Weber and Heuss (71), Oehlecker (53) and Griffith (62). Besredka (72) added a dilute egg infusion to the bouillon instead of glycerin. Although bovine bacilli grew better on glycerinated bouillon than on solid glycerinated media, the Besredka medium was much superior to the glycerinated bouillons for bovine bacilli. Loewenstein's medium (73) without glycerin and with a low percentage of glycerin (0.75 per cent) has been used successfully by Jensen and Frimodt-Møller (74) and Holmes (75). In 1928 Sweany and Evanoff (76) added approximately 3 per cent butter fat in the form of cream to a combination of Petroff's egg medium (77) and Petragnani's milk medium (78), and in 1930 (79) they simplified the method for isolating bovine bacilli. It has since been further simplified and improved by Feldman (80) and Arena (81). The latter has reported favorable results with a combination of the best features of the egg-milk-cream medium with potato extract. The Bordet-Gengou medium has been recommended by Mihailescu (82) for isolating bovine bacilli, and McCarter (83) has recently emphasized the use of egg-yolk for the same purpose.

#### EXPERIMENTAL

There were several possible objectives to be obtained in this study.

The primary aim was to formulate a simplified method of typing strains of tubercle bacilli. In addition it was desirable to know the types of bacilli recovered in the various specimens studied.

Another feature was to explore the methods for culturing the bovine type of tubercle bacilli. Owing to the fact that the isolation of bovine bacilli has

generally been rather uncertain and that the percentage recovery of strains is rarely consistent with the gross pathological findings in the same specimens, it was thought to be advantageous to use many different culture media and many bottles of each one.

Finally, as a collateral observation, the efficiency of each culture medium could be determined by comparing the results of growth on the various media.

#### MATERIAL

Cultures were obtained from a wide range of sources, including material from human beings, cattle, hogs, sheep and various other animals which were placed at our disposal.

The material from cattle, hogs and sheep was obtained from the Union Stock Yards of Chicago.<sup>4</sup> The lesions from the other animals were from Chicago's Zoological Gardens,<sup>5</sup> while the few human control specimens were from old calcified lesions in various stages of healing.

#### METHODS

A small piece of tissue, usually containing tubercles, was cut from the organ, with sterile instruments and ground in sterile mortars to a soft mash. Enough sterile water was added to permit of emulsification—usually about 5 cc. was required. About 5 cc. of the emulsion was then treated for thirty minutes in a 15 cc. centrifuge tube with an equal quantity of 5 per cent oxalic acid, and incubated for twenty-five minutes. The sediment was then thrown down by centrifugation, neutralized and spread evenly with a 4 mm. platinum loop over the surface of several bottles of each medium. A total of 16 different media were used, but not all at the same time. Observations for growth were made every week.

A representative number of culture growths and all growths in which there was any doubt as to their identity were inoculated into animals.

Each culture was usually inoculated as moist culture into guinea pigs in 1.0 mg. dosage. Wherever indicated, rabbits were given intravenously 0.1 mg. and chickens 1.0 mg. If there were any questionable reactions in the large dosage we reduced the amount in each to 0.1 mg. for the guinea pig and 0.01 mg. for the rabbit. Most of the cultures produced clear-cut findings in their reactions in the animals. One avian type culture at first had a slight virulence for guinea pigs and a slightly reduced virulence for chickens. Two bovine cultures produced a few colonies on the glycerin media. Bovine bacilli may vary in glycerophilism. It has been shown by Arena (81) that passage of bovine bacilli into human beings augments the glycerophilism but does not change the reaction in test animals. Guinea pig passage also increased glycerophilism; in fact, guinea pig passage used to be necessary in order to isolate bovine cultures on glycerinated medium, but all typical strains may be identified in rabbits. Until more refined methods

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<sup>5</sup> Mr. Floyd S. Young, Zoological Gardens, Lincoln Park, Chicago. The authors are grateful to both Dr. Bengston and Mr. Young for their coöperation.



are devised the atypical and avirulent strains must remain difficult problems, if not total enigmas.

#### RESULTS OF GROWTH AND RELATIVE EFFICIENCY OF MEDIA EMPLOYED

Along with the isolation of cultures from the various organs and tissues the results of the growths are shown in table 1. The numerical values at the bottom

TABLE 1

	1	4	S-G	5	7	6	8	2	3	3A	9	S	P	L	WP
Percentages of ingredients by volume															
Yolk.....	23.3	24.9	27.2	33.1	33.1	33.1	33.1	42.5	43.2	43.2	48.4	26.3	22.4	23.3	28.9
White.....	38.4	40.9	35.2	32.7	32.7	32.7	32.7	19.2				34.0	36.7	38.4	31.1
Milk.....	27.8	23.0	35.4	23.0	23.0	23.0	23.0	27.8	46.3	46.3	48.4	34.3	36.8		
Cream.....	9.3	9.9		9.9	9.9	9.9	9.9	9.3	9.3	9.3					
Glycerin....												3.3	2.9	0.7	4.8
2% Mala- chite green solution..	1.2	1.3	2.2	1.3	1.3	1.3	1.3	1.2	1.2	1.2	3.2	2.1	1.2	1.2	1.0
Water.....														36.4*	35.2
Percentages of dry ingredients by weight															
Peptone....													0.2		
Potato flour.....	1.8		2.2			1.9		1.85	1.85	1.85		2.2	1.5	1.8	
Fresh potato**.							19.7						18.0		12.5
Asparagin..	0.18		0.2		0.19	0.19	0.19	0.18		0.18		0.2		0.2	
Inverse efficiency.	7.3	6	5.4	5.4	4.6	4.0	3.4	2.5	3.0	1.8	7.5				

\* % of salts in total media of Lowenstein.

K<sub>2</sub>SO<sub>4</sub> —.148%. Mg citrate .037%. MgSO<sub>4</sub> —.014%.

\*\* The exact volume is difficult to determine in these media.

The numbers represent different varieties of egg-milk media.

S, P, L, WP, S-G represent Saenz, Petregnani, Loewenstein, Woolley-Petrik, Saenz without glycerin, respectively.

of each column indicate in inverse proportion the growth efficiency, based on the size and number of colonies and the speed of growth.<sup>6</sup>

<sup>6</sup> Each colony up to 25 was given one point. From 25 to 50 colonies (+) was 25 points; 50-75 (++) was 50 points; 75-100 (+++) was 75 points; and over 100 (++++) was 100 points. Sixty per cent of every weekly increase was added. That is, if the result changed from a ++ to a +++ the increase was 60 per cent of the 25 point difference, or 15 points. Every table was thus recorded numerically, the results for each medium were totaled, averaged and arranged in the order of growth efficiency as first, second, third place, etc. Then the "place" figures for each medium were totaled and averaged.

Modification 2 seems to indicate that an egg-yolk content of about 50 per cent is necessary for the best results. The small amount of egg-white used not only fails to detract from the results, but it seems to give the medium a better texture. In modification 3 the egg-white was replaced by milk with no significant improvement in the culture growths. Asparagin, in 3A and 7, however, seems to give slightly better results than those obtained without it in modification 3 and 5, respectively. The need of potato appears to be demonstrated in the poorer growth on potato-free preparations 4, 5, 7 and 9. Fresh potato bouillon, as shown in modification 8, is slightly better than the potato flour as shown in no. 6. Medium no. 9, with only egg-yolk and milk, was inadequate, besides the resulting medium tended to dry out too soon. Modifications 1, 4, 5, 6, 7 and the Saenz medium without glycerin were distinctly inferior to the others.

There was little to choose between the different media containing glycerin, although no direct comparisons were made due to the fact that all four were rarely used at one time. The Loewenstein medium contains a mixture of salts which is partly supplied by the milk in the Saenz and Petragnani media. The latter and the Woolley-Petrik medium call for fresh potato which Arena has also used to advantage. The potato which supplies starch and protein also would supply an undetermined amount of salts.

Although cream is a distinct advantage in producing growth of the bovine types, it is apparently of no advantage for growing the human and avian strains.

*Type of tubercle bacilli isolated from specimens:* The majority of specimens had typical lesions ranging in size from a few millimeters to 2 cm. in diameter. In some specimens only a few lesions were found.

Of 57 specimens from animal organs obtained from the Stock Yards, growth was obtained on 52 (91.2 per cent). Only one group of organs (1.99 per cent) was negative on culture out of the total of 53 in which gross tubercles were found, giving a value of 98.1 per cent positive cultures on specimens with gross lesions. The results on 19 of these 57 specimens are recorded in chart 1, together with the results on 2 specimens obtained from primates and 5 from human material. For the other 33 Stock Yards specimens from which bacilli were recovered, only the resulting type is given, as determined by culture and guinea pig inoculation.

In the total of 59 positive specimens, 7 human, 16 avian and 36 bovine strains were recovered and typed.

From 33 hog specimens growth was obtained in 28, consisting of 16 avian and 12 bovine strains. Four of the negative specimens did not reveal tubercles on gross examination. Inasmuch as many hogs have involvement only in the cervical region, it is possible that the spleens and livers did not contain bacilli. The 24 bovine specimens all yielded cultures and all were of the bovine type.

The exact number of separate carcasses from the Stock Yards is not known, because on some occasions several organs were delivered in one container. Unless the organs were held together by tissue strands the number of carcasses was

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For example, if a medium had two first places, two second places and a sixth place, there would be a total of 12 for 6 culture growths, giving an average of 2, which is the efficiency number appearing at the bottom of each column in the table.

NO	SOURCE	TIME DAYS	MEDIA WITHOUT GLYCERINE							WITH GLYCERINE				ANIMALS				
			1	2	3	6	8	SG	S	P	WP	L	G	R	C			
1	<i>Tubercle</i> x359	60																HUMAN
2	<i>Tbcd</i> x483	42																
3	<i>Tbcd.</i> x 790	35																
4	<i>Tbcd</i> x169	30																
5	<i>Pleural Fl</i> (NR)	30																
6	<i>Tbcd</i> Orang Liver	28																
7	<i>Macaque</i> Abd LN	27																
8	<i>Cow Lung</i> #1-1	26																BOVINE
9	" " #1-2	52								3								
10	" " #1-3	37																
11	<i>Hog Spleen</i> #2-2	44																
12	<i>Cow Lung</i> #2-1	35	C															
13	" " #2-2	35																
14	<i>Cow L N</i> #2	35																
15	<i>Cow Lung</i> #6-2	69																AVIAN
16	<i>Hog Spleen</i> #2-1	28																
17	<i>Hog Liver</i> #2-2	22																
18	<i>Sheep Lung</i> #3	30																
19	<i>Hog Spleen</i> #4-1	45																
20	<i>Hog Liver</i> #4-4	42							6			1						
21	" " #5-2	47	—	3			—	3										
22	" " #5-5	38	5				—	—										
23	" " #5-6	38					—	—						K				
24	" " #5-8	38	—									5		—	K			
25	<i>Hog Lung</i> #5-1	38					—	—										
26	" " #5-2	38					—	8										

CHART 1

#### Cultures:

The height of the black block indicates the amount of growth.

The numbers indicate the number of colonies.

C = contamination.

#### Virulence:

The height of the black block is proportional to the reciprocal of the number of days the animal lived after inoculation. In animals killed after ninety days, marked "K", the black area is placed above the base line.

The width of the black block represents the amount of gross pathological findings at death.

In the solid white squares no experiments were done The minus sign indicates no growth.

The important features are the inhibiting effect of glycerin and the adjuvant action of cream and milk on the growth of the bovine tubercle bacillus; the old and well known mild reaction of the human strain for the rabbit; and the almost negligible reaction of the avian strain for the guinea pig.

uncertain. It is conservative to say, however, that the majority of the hog specimens were avian with no human strains at all. Only avian bacilli were recovered from sheep and all human and primates studied were infected with the human type.

Acid-fast bacilli were found only on direct smear in about half the human, hog and cattle specimens. There were many bacilli in the specimens from the sheep and primates.

Chart 1 has been so arranged that the various types of tubercle bacilli will stand out in contrast to the other types. First in the order of diagnostic procedure as well as importance is the effect of glycerin in culture media on the growth of bovine bacilli. Only one growth of three colonies was obtained on glycerinated media in all of the bovine cultures shown in the chart. The remaining cultures were negative. The next in order and importance is the negligible effect of avian bacilli on the guinea pig separating out this strain from the other two. Then, to round out a triad of significant reactions, there is the time honored

TABLE 2

*A composite table showing, on the basis of a maximum of ten, the approximate differences in culture and animal reactions of the three main types of tubercle bacilli*

	CULTURE MEDIUM		ANIMAL INOCULATION WITH MASS CULTURE		
	With glycerin	Without glycerin	Guinea pig 1.0 gm.	Rabbit 0.01 mg.	Chicken 1.0 mg.
Human.....	9	7	8	1-4*	0
Bovine.....	0-2	8	10	8-10	0
Avian.....	10	9	0-1	2-8**	10

\* Few tubercles ever appear in the lungs.

\*\* The Yersin or non-nodular type of infection.

difference in the effects of the human and bovine bacilli on the rabbit, to be used if the cultures do not give a satisfactory separation.

Another observation of more than ordinary significance is the low virulence for the guinea pig of some of the strains from the old human lymph nodes compared to those found in the more active human lesions and in the strain found in the primates. This observation may have far reaching importance in understanding the pathogenesis of the disease.

In order to summarize, simplify and facilitate the typing procedure, a hypothetical tabulation is shown in table 2. The values given are approximations gained from the work of others as well as from our own experience. All reactions are based on a maximum of 10 and are a composite of all methods useful in typing.

All but a few avirulent and atypical strains of tubercle bacilli may be identified by the simplified method described.

#### DISCUSSION

It should be emphasized that there is no method which will classify every strain of tubercle bacillus, because certain strains are intermediate in nature.

Certain bovine strains, especially those recovered from human beings, guinea pigs, monkeys and perhaps other animals, as shown by Arena (81), occasionally produce a moderate eugonic type of growth on glycerinated medium. In that event a rabbit must be injected intravenously with 0.01 mg. of moist bacilli. If it is a true bovine culture the rabbit will die of a generalized tuberculosis within four to six weeks.

Occasionally a human type is "dysgonic" on glycerin medium, but if the strain is a human type the rabbit will rarely show significant disease with the dosage specified. If the strain is avian the guinea pig reaction will be negative. On extremely rare occasions avian strains may cause slight pathological changes in the guinea pig. To confirm the type of such a microorganism a chicken may be used by injecting 1.0 mg. into the wing vein. Of the three types, only avian bacilli produce any tuberculosis in the organs of a chicken.

In addition to these different possibilities, a small percentage of avirulent and atypical strains of human and bovine tubercle bacilli have been described which do not fit into any category and may be unclassifiable. According to variations in behavior, Griffith (84) divides the two mammalian tubercle bacilli into eight groups based on a combination of growth characteristics and virulence. Gervois (85) arranges them more conveniently in only three groups, namely, typical, culturally variable with normal virulence and those with reduced virulence with or without cultural changes.

On the whole, however, atypical strains are rare. Many come from skin, bone, joint and lymph node lesions. According to Griffith (86), the more superficial the lesion, as in lupus, the greater the tendency to become avirulent or atypical, suggesting the effect of environment on the characteristics of the bacilli.

To differentiate many of these atypical strains requires extensive serological studies and even then the results may be equivocal. Many of these strains seem to be due to an unnatural environment causing variation. The origin of the tubercle bacillus was probably late in the scale of evolution and is perhaps more susceptible to change for that reason. The questions of transmutation of human to bovine by animal passage and the natural transmutation of bovine to human in the human have been debated for decades without decisive conclusions. The basic facts of variation, mutation, dissociation, degeneration or degradation of virulence of tubercle bacilli, however, are little understood at present.

Naturally, the explanation of such changes is not forthcoming now and will at no time be simple. It must involve the complicated field of genetics, as the germ plasm is played upon by the almost innumerable forces of nature, some of which may denature and others rearrange the basic molecular structure of elements concerned with heredity. These changes may well become manifest by changes in morphology, chemical behavior and virulence.

#### SUMMARY

The subject of tuberculosis as it exists in warm-blooded animals and the development of animal and culture methods for typing the three main strains of tubercle bacilli affecting warm-blooded animals has been reviewed.

A series of experiments are reported with the purpose of obtaining a maximum number of positive cultures, especially of bovine bacilli, from the organs of animals and man; and of developing a simple method for typing the bacilli isolated.

The best ingredients and combinations of ingredients observed in the various culture media used were 40 to 50 per cent egg-yolk with not over 20 per cent egg-white; 20 to 25 per cent milk, including 3 per cent of the total in butter-fat in the form of cream for bovine bacilli, or 3 to 5 per cent glycerin for human and avian bacilli; 5 to 10 per cent fresh potato mash; and 0.2 per cent asparagin. An inhibiting dye, preferably malachite green oxalate 0.03 per cent, should be used as an inhibitor of secondary microorganisms.

Of 57 specimens from stock-yard animals, growth was obtained in 52 (91 per cent).

Of 53 specimens with visible tubercles, only one was negative—a 98 per cent positive response.

Only bovine strains were found in tissues from 24 bovine specimens; and only avian bacilli were obtained from the organs and bones of a sheep. Sixteen avian and 12 bovine strains were obtained in 33 specimens from hogs. Five hog specimens were negative.

From 2 specimens from primates and 5 from man, bacilli of the human type were isolated.

It has been pointed out that the minimum of laboratory procedures for typing tubercle bacilli consists of seeding the suspected and properly treated material on at least one each of a good glycerinated and glycerin-free medium, and the inoculation of 0.1 mg. of moist culture of the bacilli into a tuberculin-negative guinea pig. The bovine bacilli do not grow or grow only sparsely on the glycerinated medium. The human and avian bacilli, on the other hand, grow better on the glycerinated medium than on the non-glycerinated medium. As shown by others, the avian strain causes no more than a local abscess when injected into a guinea pig. Other growths are the human variety or are atypical. Other atypical strains should be inoculated into rabbits which, with small doses, develop a rapidly fatal disease with the bovine but only a mild chronic disease with human strains.

#### SUMARIO

El tema de este trabajo es la tuberculosis, tal como se presenta en los animales hematermos, y la elaboración de métodos de inoculación en animales, y de cultivo para clasificar las tres principales cepas de bacilos que afectan a dichos animales.

Comunícase una serie de experimentos encaminados a obtener un número máximo de cultivos positivos, en particular de bacilos bovinos obtenidos de los órganos de distintos animales incluso el hombre, y a encontrar una técnica sencilla para clasificar los bacilos aislados.

Los mejores ingredientes y combinaciones utilizados en los varios medios de cultivo fueron: 40 a 50% de yema de huevo con no más de 20% de clara de huevo: 20 a 25% de leche comprendiendo 3% del total en grasa de mantequilla en forma de crema para los bacilos bovinos, o de 3 a 5% de glicerina para los

aviarios; de 5 a 10% de patata fresca majada; y 0.2% de asparagina. Como inhibidor de los microorganismos secundarios debe utilizarse un colorante, de preferencia 0.03% de oxalato de verde de malaquita.

De 57 ejemplares procedentes de los animales de los frigoríficos, se obtuvieron colonias en 52 (91%).

De 53 ejemplares en que había tubérculos visibles sólo uno resultó negativo: 98% de positividad.

Sólo se encontraron cepas bovinas en los tejidos de 24 ejemplares de bovinos, y sólo bacilos aviarios en los órganos y huesos de una oveja. En 33 ejemplares procedentes de suinos se obtuvieron 16 cepas aviarias y 12 cepas bovinas, resultando cinco negativos.

De dos ejemplares de monos antropoides y cinco humanos, se aislaron bacilos de tipo humano.

Señálase que el mínimo de técnicas de laboratorio necesario para clasificar bacilos tuberculosos consiste en sembrar el material sospechoso y debidamente tratado, por lo menos en dos medios buenos: uno glicerinado y otro desglicerinado y en la inoculación de 0.1 mg de cultivos húmedos de los bacilos en un cobayo negativo a la tuberculina. Los bacilos bovinos proliferan muy poco o nada en el medio glicerinado, sucediendo lo contrario con los humanos y aviarios. Según han demostrado otros investigadores, la cepa aviaria no produce más que un absceso local al ser inyectada en un cobayo. Las otras colonias o pertenecen a la variedad humana o son atípicas. Deben inocularse otras cepas atípicas en los conejos, los cuales con dosis pequeñas manifiestan una afección rápidamente letal con las cepas bovinas, pero sólo crónica y leve con las humanas.

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# TUBERCULOSIS ACCORDING TO AGE, SEX, FAMILY HISTORY AND CONTACT<sup>1</sup>

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Studies of the course of tuberculosis are usually based on the experience of patients treated in sanatoria (1, 2, 3). This experience is heavily weighted with advanced cases and does not present the disease in its true perspective. It is necessary to include cases of all stages of the disease and, if an understanding of the outcome of all cases is desired, to study a series in which cases in each stage are present in more or less their true proportion.

The need for more exact knowledge concerning the outlook in cases with a limited tuberculous process is becoming greater. X-ray examinations of Selective Service registrants, of industrial and other groups, on a hitherto unparalleled scale, have been made possible by 4" by 5" and 35 mm. film. Large numbers of persons have been discovered to have minimal or latent lesions and have become a problem to physicians and public health authorities.

Data collected in the Tuberculosis Study in Williamson County, Tennessee, although not sufficient to answer finally or completely the manifold questions which arise, are nevertheless unique. This is so for two main reasons, namely: (1) all types of cases observed in an intensive study of the disease in a rural county are included and (2) the study has been maintained over a period of twelve years.

From the establishment of the study in December, 1931 to January 1, 1943, 913 white persons have been found to have reinfection type tuberculosis. In this paper, certain of the factors which are important in the study of tuberculosis, namely age, sex, family history and contact, will be considered in the analyses of subsequent course of disease. This report will be divided into the following four sections: *A.* Observed and expected deaths by age and sex; *B.* Course of disease by age and sex; *C.* Family history and contact; and *D.* Course of disease according to family history and contact.

The classification of cases into manifest and latent apical is the one recommended by Opie (4). Persons are classed as having manifest tuberculosis through findings on X-ray examination and the presence of physical signs and/or symptoms indicative of tuberculosis. They are classed as having latent apical tuberculosis when the lesions were shown only by roentgenogram without the presence of either physical signs or symptoms of the disease. The classification of lesions as minimal, moderately advanced and far advanced is in accordance with that recommended by the National Tuberculosis Association. The classification at the time of diagnosis of tuberculosis of the 913 persons entering into this study is shown in table 1 by sex.

This group of cases discovered by the study through referrals by private physicians, examinations of contacts, etc., includes 384 cases considered manifest

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active at the time of diagnosis. Of these, 89 were far advanced, 145 moderately advanced and 150 minimal. Thus, with this intensive study of tuberculosis, 39 per cent of the manifest active cases were found to be in the minimal stage. Two hundred and sixty-eight manifest cases were believed to be arrested at the time of first examination in this clinic. Since 261 persons with lesions demonstrable by X-ray examination had no physical signs nor symptoms and gave no history of illness indicative of tuberculosis, they are classed as latent apical cases. For nearly all of these, 251, the extent of the involvement corresponded to that of a minimal lesion of the manifest cases with only 10 considered moderately advanced in extent. Because of the inclusion of many minimal, minimal arrested and latent apical cases, the distribution of these 913 cases by extent and activity differs from that in areas where cases are usually discovered through examinations of persons with signs or symptoms of tuberculosis.

TABLE 1

*Classification on diagnosis of 913 persons with pulmonary tuberculosis, by sex*

CLASSIFICATION ON DIAGNOSIS	TOTAL		MALE		FEMALE	
	Number	Per cent	Number	Per cent	Number	Per cent
Total.....	913	100.0	360	100.0	553	100.0
Far advanced.....	89	9.7	39	10.8	50	9.0
Moderately advanced.....	145	15.9	75	20.8	70	12.7
Minimal.....	150	16.4	50	13.9	100	18.1
Far advanced arrested.....	1	0.1	1	0.3	—	—
Moderately advanced arrested.....	39	4.3	19	5.3	20	3.6
Minimal arrested.....	228	25.0	76	21.1	152	27.5
Latent apical.....	261	28.6	100	27.8	161	29.1

The number of females exceeded the number of males in this group of cases of tuberculosis (553 females and 360 males). This excess was large in the minimal, minimal arrested and latent apical groups. In the interpretation of the findings by sex, this difference should be considered. Although part of the difference may be attributed to the reluctance of males to be examined, this is not believed to account for all of the difference. The number of deaths considered due to tuberculosis (8) from 1932 to 1941 of white females (66) also exceeded the number of deaths of white males (53). Therefore, it is likely that there is more tuberculosis in the female population of the county.

In table 2, the 913 cases of tuberculosis are tabulated to show (a) the clinical classification at the time of first examination and (b) the status of these cases on January 1, 1943. The period of observation of these persons with tuberculous lesions varies from a few months to over eleven years. From these data, without consideration of the period of observation, it is evident that the disease has progressed more frequently in those with moderately advanced or far advanced

tuberculosis than in the other groups. The data, however, require a more exact analysis taking into account the period of observation with evaluation of many factors.

#### A. OBSERVED AND EXPECTED DEATHS BY AGE AND SEX

For the determination of the risk of mortality, the deaths actually observed in the persons of each classification are compared with the number of deaths from all causes which would have occurred had these people suffered the mortality rates prevailing in the white population of Tennessee. Account has been taken of the period of observation, age and sex of the 913 persons with reinfection type tuberculosis. The average annual age-specific death rates of the white population for the midperiod (1936-1938) were then applied to the person-years of life experience

TABLE 2

*Classification on diagnosis of 913 persons with tuberculosis, and status as of January 1, 1943*

CLASSIFICATION ON DIAGNOSIS	TOTAL	STATUS JANUARY 1, 1943									
		Dead		Active			Arrested			Latent apical	Re-moved
		Tuberculosis	Other causes	Far advanced	Moderately advanced	Minimal	Far advanced	Moderately advanced	Minimal		
Total.....	913	104	91	18	56	29	6	63	234	150	162
Far advanced.....	89	65	1	6	—	—	4	3	—	—	10
Moderately advanced.....	145	32	22	6	36	—	1	26	1	—	21
Minimal.....	150	2	12	5	7	24	1	3	53	—	43
Far advanced arrested.....	1	—	—	—	—	—	—	—	—	—	1
Moderately advanced arrested..	39	2	5	1	—	—	—	26	—	—	5
Minimal arrested.....	228	2	20	—	8	1	—	3	162	—	32
Latent apical.....	261	1	31	—	5	4	—	2	18	150	50

in each age and sex group to obtain the expected number of deaths. This section of the report deals with the comparison of the observed and expected deaths of persons according to classification on diagnosis.

The data have been combined and the total experience is shown in table 3. In all, these 913 persons contributed 4,728.5 years of experience or an average of 5.2 years of observation per person. Since many of the patients with far advanced and moderately advanced tuberculosis died within a few years after discovery, the average periods of observation were shorter for these two groups than for the others.

The ratios of the observed to expected deaths vary according to the classification on diagnosis. Sixteen times as many deaths were observed as expected among those far advanced and 4.1 times as many among those moderately ad-

vanced. For the other groups, however, 75 deaths occurred and 76 were expected. Thus, patients with minimal, arrested or latent apical tuberculosis do not appear to have been at greater risk of death than was the general white population of Tennessee.

These ratios of observed to expected deaths for patients far advanced and moderately advanced on diagnosis are lower than those observed in other areas. For example, in Cattaraugus County, Downes (5) noted forty-eight times as many deaths as expected for those far advanced and ten times as many as expected for those moderately advanced. To understand the cause of the differences these ratios require further study by age and sex groups.

The comparison of observed and expected deaths for persons in the two clinical groups (far advanced and moderately advanced) in table 4 reveals the great difference in the ratios in three age groups. For persons under 35 years of age,

TABLE 3

*Deaths from all causes and from tuberculosis and the expected deaths according to classification on diagnosis*

CLASSIFICATION ON DIAGNOSIS	PERSON-YEARS OF LIFE EXPERIENCE	DEATHS		EXPECTED DEATHS—ALL CAUSES	RATIO OBSERVED ÷ EXPECTED
		All causes	Tuberculosis		
Total.....	4,728.5	195	104	93.0	2.1
Far advanced.....	225.5	66	65	4.1	16.1
Moderately advanced.....	512.5	54	32	13.2	4.1
Minimal.....	731.0	14	2	12.5	1.1
Far advanced arrested.....	3.5	—	—	0.1	
Moderately advanced arrested.....	168.5	7	2	7.8	0.9
Minimal arrested.....	1,434.0	22	2	30.3	0.7
Latent apical.....	1,653.5	32	1	25.0	1.3

a period of life when mortality rates are low, many times as many deaths were observed as expected with a ratio of 92 for the far advanced and 24 for the moderately advanced. For persons in the oldest age group, 55 years and over, an age period in which death rates from all causes are high, the ratios were relatively low. These observations are in line with clinical impression although the extent of the differences may not have been appreciated.

The experience of Downes consists of a younger group of patients than does the Williamson County experience. Slightly over half of the years of observation of persons in her experience (51 per cent for moderately advanced and 54 per cent for far advanced) were of patients under 35 years of age. In our experience only 20 per cent of the person-years of observation of the moderately advanced and 36 per cent of the far advanced were in that age group. Thus, the difference in the ratios is largely accounted for by this difference in age of persons known to have tuberculosis and under observation.

In Tennessee, new cases of tuberculosis are discovered in persons of all adult

age groups with a surprising number in persons over 55 years of age. In other areas patients found to have tuberculosis appear on the average to be younger. A similar difference is seen in tuberculosis death rates; the death rates are higher in the older age group in Tennessee than are the comparable rates in the United States. Demographic, bacteriological and clinical evidence from Williamson County indicates the accuracy (8) of the Tennessee death rates.

TABLE 4

*Deaths from all causes and from tuberculosis and the expected deaths by age groups for those far advanced and moderately advanced on diagnosis*

AGE GROUP	FAR ADVANCED					MODERATELY ADVANCED				
	Person-years of life experience	Deaths		Ex-pected deaths—All causes	Ratio Ob-served ÷ ex-pected	Person-years of life experience	Deaths		Ex-pected deaths—All causes	Ratio Ob-served ÷ ex-pected
		All causes	Tuber-culosis				All causes	Tuber-culosis		
Total.....	225.5	66	65	4.06	16	512.5	54	32	13.23	4
Under 35 years.....	80.5	24	23	0.26	92	102.0	8	8	0.33	24
35-54 years.....	65.5	15	15	0.46	33	154.0	10	8	1.20	8
55 years and over.....	79.5	27	27	3.34	8	256.5	36	16	11.70	3

TABLE 5

*Deaths from all causes and from tuberculosis and the expected deaths by sex and age group for patients far advanced on diagnosis*

AGE GROUP	MALE					FEMALE				
	Person-years of life experience	Deaths		Ex-pected deaths—All causes	Ratio Ob-served ÷ ex-pected	Person-years of life experience	Deaths		Ex-pected deaths—All causes	Ratio Ob-served ÷ ex-pected
		All causes	Tuber-culosis				All causes	Tuber-culosis		
Total.....	100.5	30	29	1.98	15	125.0	36	36	2.08	17
Under 35 years.....	32.5	9	8	0.12	75	48.0	15	15	0.14	107
35-54 years.....	32.0	6	6	0.24	25	33.5	9	9	0.22	41
55 years and over.....	36.0	15	15	1.62	9	43.5	12	12	1.72	7

Another variable in addition to age considered in this study of the course of disease is sex of the patient. For those far advanced and moderately advanced the data are shown by sex as well as age in tables 5 and 6.

In the two age groups, under 35 years of age and 35 to 54 years of age, the ratios of observed to expected deaths are somewhat higher for females than for males. For the older persons in the age group 55 years and over the ratios of observed to expected deaths were approximately the same for both sexes. From this comparison of observed and expected deaths, it appears that the young adult female with advanced tuberculosis is slightly less able to prevent progress of the tuberculous process. The young adult male, however, fares slightly better. In the older age group no difference was noted for males and females.



When mortality from tuberculosis in Tennessee is viewed by age and sex, similar sex differences are seen. In young adult life the death rates from tuberculosis are high at an earlier age for females than for males. For the three-year period 1938 to 1940, the tuberculosis death rate in white females in the 15 to 19 year age group was over twice the male rate. In the next three five-year age groups, also, the rates for females were high and were higher than the comparable male rates. For the age group 35 to 54 years, however, the male rate exceeded the female. In the oldest age group studied at this time, 55 years and over, the death rates were practically the same for white males and females. Therefore, these ratios of observed to expected deaths in young adult life and in the older age group by sex are consistent with tuberculosis death rates in the white population of Tennessee.

From this comparison of observed and expected deaths it is seen that only in two clinical groups, far advanced and moderately advanced, is there any increase in the death rate. For these two clinical classes, sixteen times and four times

TABLE 6

*Deaths from all causes and from tuberculosis and the expected deaths by sex and age group for patients moderately advanced on diagnosis*

AGE GROUP	MALE					FEMALE				
	Person-years of life experience	Deaths		Ex-pected deaths—All causes	Ratio Ob-served ÷ ex-pected	Person-years of life experience	Deaths		Ex-pected deaths—All causes	Ratio Ob-served ÷ ex-pected
		All causes	Tuber-culosis				All causes	Tuber-culosis		
Total.....	283.5	26	15	7.34	4	229.0	28	17	5.89	5
Under 35 years.....	44.0	3	3	0.16	19	58.0	5	5	0.17	29
35-54 years.....	98.0	5	3	0.82	6	56.0	5	5	0.38	13
55 years and over.....	141.5	18	9	6.36	3	115.0	18	7	5.34	3

as many deaths were observed as expected. For young adults under 35 years of age the ratios were very high with ninety-two times as many deaths as expected for those far advanced on diagnosis and twenty-four times for those moderately advanced. The mortality of young persons with advanced tuberculosis on discovery is great. For the older adults, however, the ratios were relatively low. Thus, age is an important factor to be considered in the prognosis. Sex differences were also evident, with a greater excess of deaths in the young females with advanced tuberculosis than in young males. The young females appear to show less resistance than the young males. Therefore, in considering the prognosis, the stage of the disease on discovery, age and sex of the patient are important factors.

#### B. COURSE OF DISEASE BY AGE AND SEX

The data given in the preceding section show the differences in mortality according to clinical class but fail to show other changes as improvement and retro-

gression of cases. This section, however, considers the status of these individuals known to have tuberculous lesions over a period of time.

The changes in status to be studied are of the following types:

1: Dead.

2: Retrogressed. This refers to a change to more extensive disease, for example, from moderately advanced to far advanced, from minimal to moderately or far advanced, from an arrested lesion to an active one, or from latent apical to manifest active tuberculosis.

3: Improved. This refers to a change from an active lesion to apparently arrested or to one indicating a less extensive lesion.

The final change during a year takes precedence in this analysis with death taking precedence over retrogression.

In the calculation of rates of change, it is necessary to take account of the time during which each person remained under observation. For this accounting a modification of the conventional life table is used. Since this technique has been described in detail in previous papers (6, 7) only its main features are given here. The probability of dying during each year of observation is obtained first and, from the product of probabilities of surviving each year, the probability of surviving to the end of the first, second, third, fourth, etc. years is calculated. By subtraction, the cumulative probability of death by the end of these periods of time is obtained. In addition to these risks of death the experience with regard to other changes is desired. In this calculation the proportions of the examined survivors who retrogressed and improved are applied to the survivors at risk. After retrogression or improvement the person is excluded from the experience. A correction factor is introduced to account for deaths among those already improved or retrogressed. Only the results of the application of this method with the percentages in each one of the groups are presented here.

The preceding section shows the need of consideration of age and sex of the patient in comparing observed and expected deaths. Therefore, in considering the subsequent course of the disease, the data for each sex are divided into two age groups—under 45 years of age and 45 years of age and over—for the study of the effect of age. This division of the experience into four groups is all that the data permit at this time. Although some of the persons have been followed for over eleven years, the experience was not great enough in the seventh through eleventh year to be included here. Only changes during the first six years after diagnosis are considered at this time.

The experience in some of the groups is limited and the results alone are not conclusive. They do indicate, however, the direction of the change and by reasoning from the whole experience we note there are differences. This analysis also serves to show the need of consideration of many factors in the prognosis on discovery of tuberculous lesions.

Only two types of changes can occur for those far advanced on diagnosis—death and improvement. Table 7 shows the status of the patients with far advanced tuberculosis at the end of six years after diagnosis. Of those under 45 years of age, 70.5 per cent, and of those 45 years of age and over, 85.7 per cent

were dead. Although the percentage dead was larger for the older age group than for the younger, the preceding section has indicated that there was a greater excess in observed over expected deaths in the younger group.

In the younger age group 16.1 per cent improved while but 4.1 per cent in the older age group showed improvement. The younger males appeared to do better than the younger females, a finding consistent with that from observed and expected deaths. In all groups, however, the risk of death is great for those with far advanced disease on diagnosis; the prognosis is unfavorable.

For persons with moderately advanced tuberculosis, three types of changes can occur—death, retrogression to far advanced disease and improvement. The young adults with moderately advanced disease experienced an unfavorable

TABLE 7

*Status of persons with far advanced tuberculosis on diagnosis, six years later, for two age groups by sex on basis of 100*

SEX	UNDER 45 YRS OF AGE				45 YEARS OF AGE AND OVER			
	Total	Dead	Improved	Unchanged	Total	Dead	Improved	Unchanged
Total.....	100.0	70.5	16.1	13.4	100.0	85.7	4.1	10.2
Male.....	100.0	67.3	25.9	6.8	100.0	88.3	—	11.7
Female.....	100.0	73.1	6.3	20.6	100.0	83.7	10.1	6.2

TABLE 8

*Status of persons with moderately advanced tuberculosis on diagnosis, six years later, for two age groups by sex on basis of 100*

SEX	UNDER 45 YEARS					45 YEARS AND OVER				
	Total	Dead	Retrogressed	Improved	Unchanged	Total	Dead	Retrogressed	Improved	Unchanged
Total.....	100.0	36.3	37.9	23.1	2.7	100.0	50.8	5.0	34.1	10.1
Male.....	99.9	33.3	40.5	26.1	—	100.0	46.9	8.8	36.4	7.9
Female.....	100.0	38.0	38.2	12.2	11.6	100.0	53.5	—	33.0	13.5

course of disease. In addition to 36.3 per cent dead, 37.9 per cent retrogressed to far advanced, giving, in all, 74.2 per cent with an unfavorable outcome. In the older age group (45 years and over) the lesions appeared to be more stable with 10.1 per cent remaining unchanged and 34.1 per cent classed apparently arrested.

The preceding section indicates that the observed and expected deaths are very nearly the same for persons with minimal, minimal arrested and latent apical tuberculosis. Therefore, mortality as given in the next three tables is not an index of an unfavorable course of disease but rather it is the expected occurrence with account taken of age and sex.

In general, persons with minimal tuberculosis on diagnosis experience a favor-

able course with 75.0 per cent of those under 45 years of age improved to an apparently arrested stage by the end of six years. In the older group, 66.0 per cent were considered apparently arrested in this period of time. A slightly greater proportion of those in the younger group than in the older group retrogressed to a moderately advanced or far advanced stage. The number of males with minimal tuberculosis is small. In both age groups the males retrogressed more frequently than did the females. This may be in part accounted for by the inclusion of more females than males with very limited lesions of slight significance.

TABLE 9

*Status of persons with minimal tuberculosis on diagnosis, six years later, for two age groups by sex on basis of 100*

SEX	UNDER 45 YEARS					45 YEARS AND OVER				
	Total	Dead	Retro- gressed	Im- proved	Un- changed	Total	Dead	Retro- gressed	Im- proved	Un- changed
Total.....	100.0	—	25.0	75.0	—	100.0	20.8	13.2	66.0	—
Male.....	100.0	—	58.8	41.2	—	100.0	37.8	20.7	41.5	—
Female.....	100.0	—	16.2	83.8	—	100.0	7.7	7.1	85.2	—

TABLE 10

*Status of persons with minimal arrested tuberculosis on diagnosis, six years later, for two age groups by sex on basis of 100*

SEX	UNDER 45 YEARS				45 YEARS AND OVER			
	Total	Dead	Retro- gressed	Unchanged	Total	Dead	Retro- gressed	Unchanged
Total.....	100.0	1.3	14.0	84.7	100.0	14.5	21.1	64.4
Male.....	100.0	—	38.4	61.6	100.0	18.4	34.5	47.1
Female.....	100.0	1.9	5.8	92.3	100.0	12.3	15.7	72.0

For persons discovered to have minimal arrested tuberculosis, only two changes can occur, death and retrogression. In this group death occurred approximately as frequently as expected. A relatively small proportion of the cases retrogressed in six years, 14.0 per cent in the younger group and 21.1 per cent in the older group (table 10). After the change to minimal active tuberculosis the progress was usually favorable with the return of an arrested process in one or two years. Here again, as with persons with minimal tuberculosis, retrogression occurred more frequently in males than in females. From the standpoint of death from tuberculosis and extension to serious tuberculosis, the discovery of minimal arrested tuberculosis in a subject in Williamson County is not indicative of serious tuberculosis in the future. Although 14.5 per cent of the persons 45 years and over were dead by the end of six years, this was expected in adults with this age and sex distribution.

Latent apical tuberculosis deserves the attention of those concerned with the control of tuberculosis. Persons with latent apical lesions are not aware of the tuberculous process, as they can give no history of illness suggestive of tuberculosis and do not show signs or symptoms of the disease. With the extension of X-ray examinations to large groups of the population, many persons will be found to have latent disease. We need to understand the significance of the discovery of latent apical tuberculosis.

In the preceding section we found that mortality was not increased among those with latent apical disease. Among the young adults, however, retrogressions to minimal or moderately advanced active tuberculosis with signs and/or symptoms occurred for 25.5 per cent (table 11). In the older age group only 8.0 per cent showed such changes in the six-year period. In this group, also, a slightly greater proportion of the males retrogressed than did the females. For the older adults, 45 years and over, the discovery of latent apical tuberculosis does not warrant alarm. The course of disease, however, is less favorable for the

TABLE 11

*Status of persons with latent apical tuberculosis on diagnosis, six years later, for two age groups by sex on the basis of 100*

SEX	UNDER 45 YEARS				45 YEARS AND OVER			
	Total	Dead	Retrogressed	Unchanged	Total	Dead	Retrogressed	Unchanged
Total.....	100.0	3.3	25.5	71.2	100.0	23.2	8.0	68.8
Male.....	100.0	4.9	27.0	67.1	100.0	28.6	11.9	59.5
Female.....	100.0	2.3	25.0	72.7	100.0	17.1	4.9	78.0

younger adults. Further subdivision of the data will probably aid in defining the exact age group of these young people who show retrogression.

From this analysis of subsequent course of the disease by age group and sex, the course of the disease is unfavorable for those moderately advanced or far advanced on diagnosis. For persons with minimal, minimal arrested and latent apical tuberculosis those in the younger age group, under 45 years of age, do not do as well as the older ones. In these three groups also the males retrogress more frequently than do females; therefore, it appears that although young males do not die from the disease as frequently as do young females, some of the males with a limited amount of tuberculosis over a period of time react unfavorably and are not able to prevent the extension of minimal lesions and the activation of minimal arrested and latent apical lesions.

### C. FAMILY HISTORY AND CONTACT

In addition to age and sex, no doubt other factors influence the course of disease. The two factors, family history of tuberculosis and household contact with persons known to have the disease, are being considered here. Although many of the persons with family histories of tuberculosis have been in contact with their

relatives, some of them report no known household contact since they were not living with the relatives at the time when they were ill with tuberculosis.

For classification of each person according to family history, the records of brothers, sisters and parents of the 913 persons included in this series were reviewed. At the time of initial examination the names, dates of birth and death and status of the parents and siblings were recorded. Many of these brothers, sisters and parents have been examined in the clinic. Some were household associates and were included in the households being followed. Others, although separated from the persons found to have tuberculosis, were examined in the clinic for various reasons. A family history of tuberculosis as used in this analysis means a case of tuberculosis in parents and/or siblings, obtained from history given by the person with tuberculosis or obtained from examination records by the study.

A history of household contact with a tuberculous patient is also obtained at the time of initial examination. Through the discovery of cases among household associates additional information regarding contact has been obtained. In this discussion only household contact prior to the onset of the disease in the case in this series is included. For individuals with latent apical tuberculosis this refers to contact in the past prior to the discovery of the lesion.

The summaries of family history and contact for the 913 individuals with tuberculosis are given in tables 12 and 13. As in the previous section the material is presented for two age groups—under 45 years and 45 years of age and over. Data regarding contact with tuberculosis and history of tuberculosis in parents and/or brothers and sisters are more complete and accurate for the younger group than for the older. A few of those in the older age group have probably forgotten contact within the household. Also they may not have known that a brother, sister or parent suffered from tuberculosis, either in the household or in another household. The data in these two tables are minimal figures.

Of the 455 persons under 45 years of age, 289, or 63.5 per cent, have brothers, sisters and/or parents known to have had tuberculosis. One-hundred and eighty-seven of these had household contact with a person with tuberculosis and 102 were not known ever to have had such contact. An additional 41 reported contact but no family history. Only 119, or 26.2 per cent, gave no family history nor contact with tuberculosis. The large number known to have a family history and/or contact is probably in part due to the extent of the tuberculosis work in the county. Several thousands have been examined in the clinic and lesions of limited extent as well as serious lesions have been discovered. In the usual clinical experience the percentages with such histories would be smaller.

For the older age group, 45 years of age and over, a higher percentage (32.1) did not know of tuberculosis in parents and/or siblings or contact with tuberculosis. The percentages of these subjects with family histories and/or contact, however, were high as in the younger age group.

Slight differences are noted in the percentages according to classification on diagnosis. Persons with latent apical tuberculosis were often discovered because of household contact and would not be discovered as frequently without known contact.

The group of persons with known contact has been studied according to the classification of tuberculosis on diagnosis and family history (table 14). A com-

TABLE 12

*Family history of tuberculosis and contact with tuberculosis for the 455 persons with tuberculosis under 45 years of age*

CLASSIFICATION ON DIAGNOSIS	TOTAL		TUBERCULOSIS IN PARENTS AND/OR SIBLINGS				NO KNOWN TUBERCULOSIS IN PARENTS AND/OR SIBLINGS				UNKNOWN	
			Contact		No known contact		Contact		No known contact			
	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent
Total.....	455	100.0	187	41.1	102	22.4	41	9.0	119	26.2	6	1.3
Far advanced.....	50	100.0	25	50.0	10	20.0	4	8.0	11	22.0	—	—
Moderately advanced	54	100.1	21	38.9	11	20.4	3	5.6	18	33.3	1	1.9
Minimal.....	93	100.1	40	43.0	25	26.9	6	6.5	20	21.5	2	2.2
Moderate advanced arrested.....	9	99.9	4	44.4	—	—	1	11.1	4	44.4	—	—
Minimal arrested....	84	100.0	27	32.1	25	29.8	4	4.8	28	33.3	—	—
Latent apical.....	165	99.9	70	42.4	31	18.8	23	13.9	38	23.0	3	1.8

TABLE 13

*Family history of tuberculosis and contact with tuberculosis for 458 persons with tuberculosis 45 years of age and over*

CLASSIFICATION ON DIAGNOSIS	TOTAL		TUBERCULOSIS IN PARENTS AND/OR SIBLINGS				NO KNOWN TUBERCULOSIS IN PARENTS AND/OR SIBLINGS				UNKNOWN	
			Contact		No known contact		Contact <sup>1</sup>		No known contact			
	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent
Total.....	458*	100.0	139	30.3	103	22.5	41	9.0	147*	32.1	28	6.1
Far advanced.....	39	99.9	16	41.0	6	15.4	2	5.1	10	25.6	5	12.8
Moderately advanced	91	100.1	26	28.6	21	23.1	7	7.7	33	36.3	4	4.4
Minimal.....	57	100.0	17	29.8	12	21.1	2	3.5	21	36.8	5	8.8
Moderately advanced arrested.....	30	100.0	9	30.0	9	30.0	2	6.7	9	30.0	1	3.3
Minimal arrested....	144	100.0	35	24.3	39	27.1	10	6.9	53	36.8	7	4.9
Latent apical.....	96	100.1	36	37.5	16	16.7	18	18.8	20	20.8	6	6.3

\* Includes one far advanced arrested on diagnosis with no history of contact nor family history of tuberculosis.

parison of the findings of this group with known contact seems permissible although the group with no known contact is not equally complete since latent apical cases would not be discovered. A difference in the classifications of

these cases is noted, dependent on whether or not the individual had a family history of tuberculosis in parents and/or siblings. Of the 187 persons under 45 years of age from families in which parents and/or brothers or sisters had the disease, 86, or 46.0 per cent, had manifest active tuberculosis, 31, or 16.6 per cent, had manifest arrested tuberculosis, and 70, or 37.4 per cent, had latent apical disease. In the group of persons with contact without known tuberculosis in family a somewhat smaller percentage had active tuberculosis, 31.7, and a larger percentage latent apical tuberculosis. Among those 45 years of age and over the same differences were noted, with a greater proportion of the persons without known tuberculosis in parents or siblings having latent apical disease than of those with family histories. These differences suggest that those without family histories may develop a less serious form of tuberculosis than those with family histories.

TABLE 14

*Classification on diagnosis of persons with tuberculosis known to have had contact according to family history and age group*

CLASSIFICATION ON DIAGNOSIS	UNDER 45 YEARS				45 YEARS AND OVER			
	With family history		Without family history		With family history		Without family history	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total.....	187	100.0	41	100.0	139	100.0	41	100.0
Manifest, active.....	86	46.0	13	31.7	59	42.4	11	26.8
Manifest, arrested.....	31	16.6	5	12.2	44	31.7	12	29.3
Latent apical.....	70	37.4	23	56.1	36	25.9	18	43.9

#### D. COURSE OF DISEASE ACCORDING TO FAMILY HISTORY AND CONTACT

To understand the rôle that the factors family history and contact play in the course of disease, the status of cases is studied for persons in these groups. Unfortunately, the additional subdivision of the material reduces some of the groups to such an extent that calculation of rates is inadvisable. The division into the two age groups—under 45 years and 45 years and over—seems necessary. Only in three groups, minimal, minimal arrested and latent apical, for those under 45 years of age are the numbers sufficient for calculations. Even here only three groups could be studied, namely, (1) family history of tuberculosis and household contact, (2) family history of tuberculosis and no known household contact and (3) no family history of tuberculosis and no known household contact.

In all groups the numbers of females exceed the numbers of males. There is no concentration of males or females in any specific group. Since the distribution by sex is not such as would bias the results, in this analysis of course of disease the data have been combined by sex in the three groups.

The status of these individuals under 45 years of age six years after diagnosis varied according to family history and contact (table 15). For those minimal on diagnosis, 35.0 per cent of those with family histories of tuberculosis and contact with tuberculosis, 22.7 per cent of those with family histories and no known



contact and none of those without family histories and with no known contact retrogressed by the end of six years after diagnosis. For those minimal arrested on diagnosis also, persons with family histories and contact did not fare as well as those without such histories. No retrogressions were noted for those without family histories or contact prior to discovery of latent apical tuberculosis.

From the consistency of these findings for the three groups, minimal, minimal arrested and latent apical, the course of the disease seems to be unfavorable for those with family histories and contact and favorable for those with no known tuberculosis in siblings or parents and with no known contact.

The data are not sufficient, however, for evaluation of these two factors and the relative importance of each. They do suggest that individuals with family histories of tuberculosis even without known household contact do somewhat worse than do those without family histories and with no known contact.

TABLE 15

*Status of persons under 45 years of age with minimal, minimal arrested and latent apical tuberculosis on diagnosis, six years later, according to family history and contact on basis of 100*

FAMILY HISTORY OF TUBERCULOSIS, CONTACT WITH TUBERCULOSIS	MINIMAL				MINIMAL ARRESTED			LATENT APICAL		
	Dead	Retrogressed	Improved	Unchanged	Dead	Retrogressed	Unchanged	Dead	Retrogressed	Unchanged
(1) Family history, contact.....	—	35.0	65.0	—	—	35.3	64.7	—	39.8	60.2
(2) Family history, no known contact.....	—	22.7	77.3	—	—	—	100.0	3.3	8.8	87.9
(3) No family history, no known contact.....	—	—	100.0	—	3.7	6.0	90.3	9.8	—	90.2

In addition to knowledge of household contact prior to onset of disease (for latent apical lesions prior to discovery by examination) contact during the period of observation has been suggested as being an important factor in the breakdown with active disease or extension of the lesion. The group of persons with latent apical tuberculosis with family histories and known contact was large enough for further subdivision (group 1). The course of disease among these 70 persons with latent apical tuberculosis may be studied according to contact during the period of observation. Of these, 15 had contact with a patient with sputum-positive tuberculosis during observation, 30 had contact with a patient with tuberculosis not known to be sputum-positive, 19 did not have any known contact in the households in which they lived and were observed, and 6 were not in households and accurate data on contact during observation were not available. Although the numbers in these groups are small it is of interest that retrogressions occurred in all three groups; the rates are as follows: 32.7 per cent for those with sputum-positive contact during observation; 43.7 per cent for those with

other contact during observation; 32.0 per cent for those with no contact during observation. At least it can be said that retrogressions occur without known household contact with tuberculosis.

Among those with minimal and minimal arrested tuberculosis, with family history and household contact prior to onset of the disease, retrogression of the minimal cases to moderately advanced or far advanced and change from arrested to active occurred in those without household contact during observation as well as in those with household contact. Although the data are not sufficient for calculation of rates, from the consistency of this observation in the subdivision of these three groups, household contact during observation does not appear to be a necessary factor for the retrogression of the case.

#### SUMMARY

1. The subsequent course of tuberculosis for 913 white persons found to have reinfection type tuberculosis in Williamson County, Tennessee has been studied. Age, sex, family history and contact of these persons are considered.

2. From a comparison of observed and expected deaths it was found that only in the two clinical groups, far advanced and moderately advanced on diagnosis, is there a larger death rate than expected. For these two clinical classes sixteen times and four times as many deaths were observed as expected. For the other groups, 75 deaths occurred and 76 were expected.

3. The course of disease was unfavorable for those moderately advanced and far advanced on diagnosis. For those with minimal, minimal arrested and latent apical tuberculosis, those in the younger age group—under 45 years—do not fare as well as the older ones. In these three groups the males retrogress more frequently than do females.

4. Of the 455 persons with tuberculosis under 45 years of age, 289, or 63.5 per cent, have brothers, sisters and/or parents known to have had tuberculosis. Of these, however, 102 were not known to have had contact with their siblings or parents when they had tuberculosis. Only 119, or 26.2 per cent, gave no family history nor household contact with tuberculosis.

5. Of the persons with tuberculosis known to have had household contact, those without family histories had latent apical tuberculosis more frequently than those with family histories. The differences suggest that those without family histories may develop a less serious form of tuberculosis than those with family histories.

6. From the consistency of retrogression rates for the three groups, minimal, minimal arrested and latent apical, the course of the disease seems to be unfavorable for those with family histories and contact and favorable for those with no known tuberculosis in parents or siblings and with no known contact.

7. Household contact during observation did not appear to be a necessary factor for the retrogression of the case. Further data are needed for evaluation of the significance of family histories of tuberculosis and contact on the course of disease.

## SUMARIO

1. Estúdiase la evolución posterior en 913 sujetos blancos en los que se descubrió tuberculosis tipo reinfección en Williamson County, Tennessee, considerándose edad, sexo, antecedentes familiares y contactos de dichos individuos.

2. Comparando la mortalidad observada y la esperada, obsérvase que sólo en dos grupos clínicos, o sean los muy avanzados y moderadamente avanzados, excede la mortalidad real a la esperada, siendo en ellos 16 y 4 veces respectivamente superior. En los otros grupos hubo 75 muertes y se esperaban 76.

3. La evolución de la enfermedad fué desfavorable en los enfermos en que se hizo el diagnóstico de moderadamente avanzados y muy avanzados. En las personas con tuberculosis mínima, estacionada mínima y apical latente, las personas más jóvenes, de menos de 45 años, no lo pasan tan bien como los más viejos. En esos tres grupos la enfermedad en el varón retrocede más a menudo que en la mujer.

4. De los 455 tuberculosos de menos de 45 años de edad, 289 (63.5%) tienen hermanos, hermanas, o padres, que se sabe han tenido tuberculosis, mas de ellos en 102 no había datos de contacto con sus hermanos o padres cuando éstos tenían tuberculosis. Sólo 119 (26.2%) no comunicaron antecedentes familiares o contacto casero con la tuberculosis.

5. De los tuberculosos en que se sabía había habido contacto casero, aquellos sin antecedentes familiares manifestaron tuberculosis apical latente, más frecuentemente que aquellos en que había tales antecedentes. Esta diferencia indica que los primeros pueden manifestar una forma menos grave de la tuberculosis que los últimos.

6. A juzgar por la constancia de los coeficientes de regresión en los tres grupos (mínimo, mínimo estacionado y apical latente), la evolución de la dolencia parece ser desfavorable en los enfermos con antecedentes y contactos familiares, y favorable en aquellos en que no existe tuberculosis conocida en los padres o hermanos, ni contacto conocido.

7. El contacto casero durante el período de observación no pareció ser un factor necesario para la regresión de la enfermedad, y se necesitan más datos para justipreciar el significado de los antecedentes familiares de tuberculosis y del contacto casero en relación con la evolución del mal.

Acknowledgment is made of the valuable suggestions of Dr. J. A. Doull.

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## PASSIVE TRANSFER OF SPECIFIC TUBERCULO-IMMUNITY AND SPECIFIC TUBERCULIN ALLERGY<sup>1, 2</sup>

H. J. CORPER AND MAURICE L. COHN

It has been shown that there are three distinct biological phenomena of singular significance in the disease tuberculosis: specific tuberculo-immunity, specific tuberculo-bacillary allergy and specific tuberculin allergy (1). A fourth phenomenon, specific tuberculin anaphylaxis, was proved to be of no appreciable practical importance in the mechanism of the disease but was of academic interest (2) and of scientific value in the evaluation of tuberculosis. The tuberculin anaphylactic hypersensitiveness in mother guinea pigs is regularly transferred to offspring born longer than a year after sensitization of the mother, and the tuberculin anaphylactic hypersensitiveness may persist in the young in demonstrable form up to at least three months after birth. It is not produced by tubercle bacilli or by tuberculosis. Tuberculin anaphylactic hypersensitiveness can be transferred passively by means of the blood from about 45 per cent of the donors (3). On the other hand, specific tuberculo-immunity, specific tuberculo-bacillary allergic hypersensitiveness and tuberculin allergic hypersensitiveness are not passed from mother guinea pigs to offspring when the mother guinea pigs are injected with viable avirulent or virulent human tubercle bacilli (4).

Since previous experiments performed by us in attempts to transfer passively specific tuberculo-immunity and specific tuberculin or bacillary allergic hypersensitiveness had not been recorded in detail, the following illustrative experiment incorporating these studies are presented in table 1. In these studies, the blood from the specifically immune and allergically hypersensitive guinea pig donors was withdrawn in about 12 cc. amounts (in sodium citrate) one and two months after vaccination. The normal recipient guinea pigs, after receiving the blood passively from the donor animals, were infected one day, one week and one month later. The grade of specific tuberculo-immunity of the donors and the grade of immunity and response to the intracutaneous tuberculin test are recorded in table 1.

Examination of the data recorded in table 1 indicates that, while the specific immune donor guinea pigs in all cases revealed a marked protection against the subcutaneous infection with virulent human tubercle bacilli, this protection was not transferred perceptibly to the normal recipient guinea pigs by giving intravenously a large amount (about 12 cc.) of the immune donor's whole citrated blood. Likewise, tuberculin allergic hypersensitiveness, as tested by the intracutaneous injection of tuberculin, was also not transferred perceptibly with the whole blood in any case.

<sup>1</sup> From the Research Department, National Jewish Hospital, Denver, Colorado.

<sup>2</sup> This investigation was aided by a gift from Morton May in memory of Florence G. May.

TABLE 1

*The passive transfer of specific tuberculo-immunity and specific tuberculin allergic hypersensitiveness in guinea pigs*

TIME AFTER VACCINATION WHEN BLOOD WAS TRANSFERRED*	TIME AFTER TRANSFUSION† WHEN INFECTED	DONORS		RECIPIENTS	
		Skin tuberculin reaction 3 days before infection‡	Organic tubercu- losis§	Skin tuberculin reaction 3 days before infection‡	Organic tuberculosis§
1 month	1 day	3	0		3
		3	0		2
		2	0		2
		3	0		3
	1 week	3	0	0	3
		4	0	0	1 (died 78 days)
		3	0	0	4 (died 96 days)
		3	0	0	3
	1 month	3	0	0	3
		3	0	0	4
		2	0	0	4
		2	0	0	4
2 months	1 day	3	0		3
		3	1		4
		3	0		4
		3	1		4
	1 week	2	0	0	3
		2	0	0	2
		2	0	0	3
		2	0	0	3
	1 month	2	1	0	3
		2	0	0	3
		2	0	0	4
		3	0	0	2
Infection controls, infected subcutaneously with 0.000,1 mg. virulent human tubercle bacilli (H160)		0	4		
		0	3		
		0	4		
		0	3		

\* All the donor guinea pigs received subcutaneously 1 mg. of viable avirulent human tubercle bacilli as designated.

† About 12 cc. of citrated whole blood obtained from the heart of the donor guinea pigs was injected intravenously (ear vein) immediately on withdrawal from the donor.

‡ For the intracutaneous test 0.001 mg. tuberculo-protein (in the natural filtrate) was given.

§ These animals were all examined 98 days after virulent infection; 0.000,1 mg. virulent human tubercle bacilli (H160) was injected subcutaneously (similar to the infection controls). The organic tuberculous involvement is graded from 0 = no macroscopic tuberculosis to 4 = a massive generalized disease of all the important organs.

## SUMMARY AND CONCLUSIONS

1. Specific tuberculosis immunity produced by means of the injection of viable avirulent human tubercle bacilli is not transferred perceptibly to normal recipient guinea pigs by the injection of citrated whole blood from the donors one month and two months after vaccination, when the specific immunity is well developed.

2. Likewise, specific allergic hypersensitiveness to tuberculin is not transferred by means of the intravenous injection of citrated whole blood from the allergic hypersensitive donors to normal recipient guinea pigs.

## SUMARIO Y CONCLUSIONES

1. La inmunidad específica a la tuberculosis producida por medio de la inyección de bacilos tuberculosos humanos avirulentos, no se transfiere perceptiblemente a los cobayos receptivos normales mediante la inyección de sangre íntegra citratada de los dadores al mes o dos meses de la vacunación, si la inmunidad específica ya está bien establecida.

2. Tampoco se transfiere a los cobayos receptivos normales la hipersensibilidad alérgica específica a la tuberculina por medio de la inyección intravenosa de sangre íntegra citratada de los donantes hipersensibles alérgicos.

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# "BERIBERI HEART" IN A TUBERCULOUS PATIENT<sup>1,2</sup>

JASON E. FARBER<sup>3</sup> AND D. K. MILLER

"Beriberi heart" is known to be associated etiologically with an unbalanced food intake or an altered metabolism, either of which may produce a thiamine (vitamin B<sub>1</sub>) deficiency (1). The condition is characterized chiefly by dilatation of the heart with cardiac failure, a normal or accelerated circulation rate, by certain electrocardiographic changes and by response to specific vitamin therapy (1, 2). The diagnosis is simplified in persons so affected if there is also present evidence of other B-complex deficiencies. Weiss (2) has shown that, in the United States, alcoholism is a significant predisposing factor in many of these individuals. In the case being reported, tuberculosis apparently was a predisposing factor.

## CASE REPORT

*Pulmonary tuberculosis, decreased food intake, glossitis, peripheral neuritis, cardiac enlargement with orthopnea, tachycardia, pulmonary congestion and electrocardiographic changes; lack of response to digitalization; treatment with thiamine and yeast followed by clinical improvement and decrease in size of heart; death three months later, autopsy.*

J. S., a fifty-six year old white laborer, was admitted from the County Infirmary, complaining of pain in the chest and lower extremities, cough and expectoration, hemoptysis, anorexia, loss of 15 lb. and dyspnea of eighteen months' duration.

On examination the patient appeared chronically ill and was bed-ridden. His tongue had a purplish color, it was heavily coated and had marginal papillary atrophy. Bronchovesicular breath sounds and râles were heard over the right side of the chest. The heart was not enlarged and no murmurs were heard. The blood pressure was 120/70. His legs showed considerable muscle atrophy. The calves were painful on palpation. There was weakness in flexing the feet against the examiner's hand. There was plantar hyperesthesia. His tendon reflexes were hyperactive.

A roentgenogram of the chest (figure 1) showed a predominantly productive tuberculous infiltration of the right lung with several areas of cavitation. The sputum was positive. The Wassermann and Kahn tests and the urine examination were negative. Examination of the blood showed a hemoglobin of 9.7 g. (67 per cent), a red cell count of 3,320,000 and a corrected sedimentation rate of 30.

The patient was kept on bed-rest, given a high caloric diet and ferrous sulfate. His temperature ranged between 97° and 100° F. and the pulse rate between 90 and 110. He frequently complained of pain in the chest and legs. His appetite gradually fell off and he became more feeble and dyspneic. At times he appeared mentally confused and depressed and wept spontaneously.

Approximately eight months after admission he appeared acutely ill, his temperature

<sup>1</sup> From the Edward J. Meyer Memorial Hospital and the University of Buffalo School of Medicine, Buffalo, New York.

<sup>2</sup> This study was aided by the Buffalo Tuberculosis Association.

<sup>3</sup> Present address: Stanford University School of Medicine, San Francisco, California.



had increased to 101° F., and his pulse rate to 120. His face appeared flushed and his tongue was red, thick and coated. He was orthopneic and cyanotic. The apex beat was best heard in the sixth interspace at the anterior axillary line. The heart tones were of poor quality but distinct, regular and rapid. No bruits were heard. The blood pressure was 110/60. Râles were heard throughout both lungs. The edge of the liver was palpable at the costal margin. There was no edema of the feet or sacrum. A roentgenogram of the chest at this time showed a considerable increase in the size of the heart. The diameter of the cardiac shadow which on admission was 10.5 cm. had increased to 18.5 cm. in

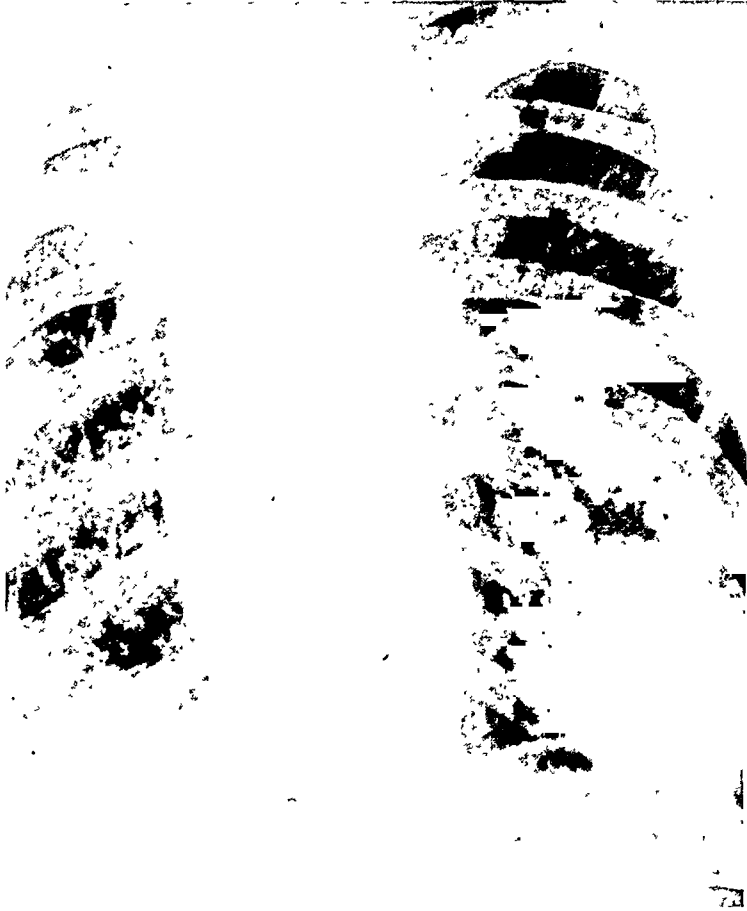


FIG. 1. Roentgenogram of the chest on admission to the hospital

transverse diameter (figure 2). There was also some clouding of the lower lung fields. To rule out the possibility of a pericardial effusion, paracentesis was done but no fluid was obtained. An electrocardiogram (figure 3) showed low amplitude, regular rhythm, sinus tachycardia and an isoelectric S-T interval in some portions of lead 3. The venous pressure was 12 cm. of water, the ether circulation time was nine seconds and the vital capacity was 1,150 cc. (best of three determinations). The hemoglobin measured 13 g. and the red blood cell count was 5,910,000. The blood sugar was 148 mg., urea nitrogen 7 mg. and serum proteins 7.5 g. per 100 cc. The patient was digitalized over a period of three days but there was no change in the clinical picture or in the size of the heart (fluoroscopically). The digitalis was discontinued.



FIG. 2. Roentgenogram showing size of the heart at the time of the acute cardiac illness

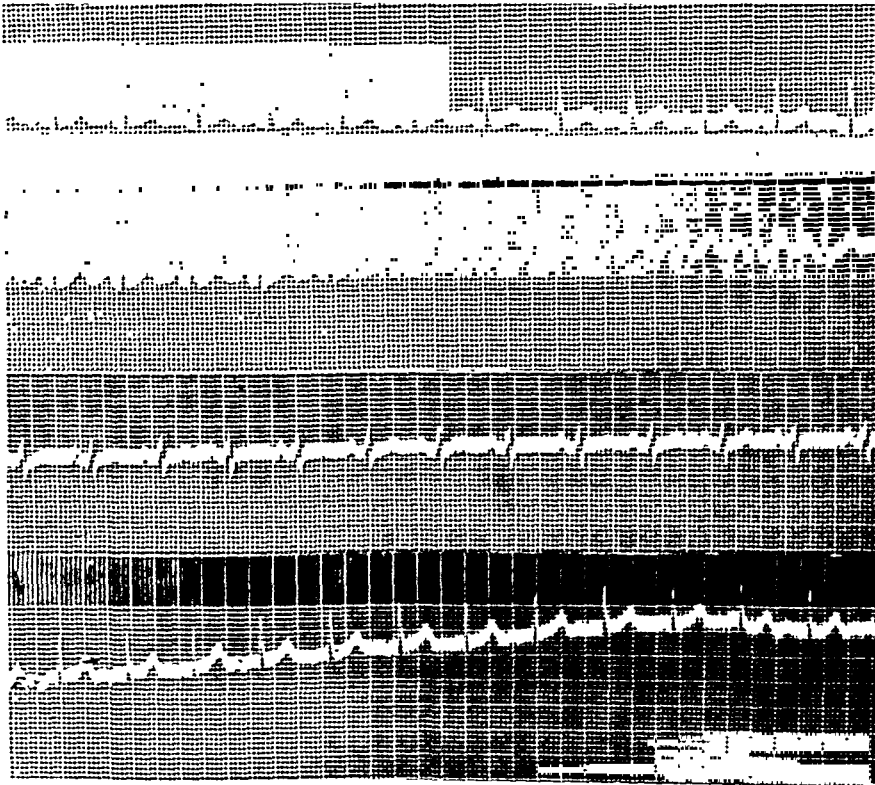


FIG. 3. Electrocardiogram. Note isoelectric S-T interval in lead 3

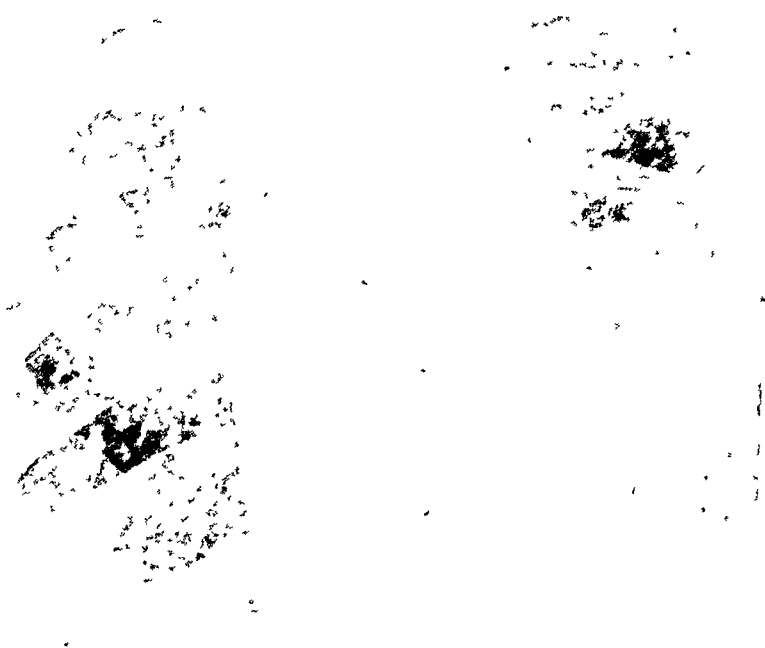


FIG. 4. Roentgenogram showing size of the heart after eighteen days of vitamin therapy.

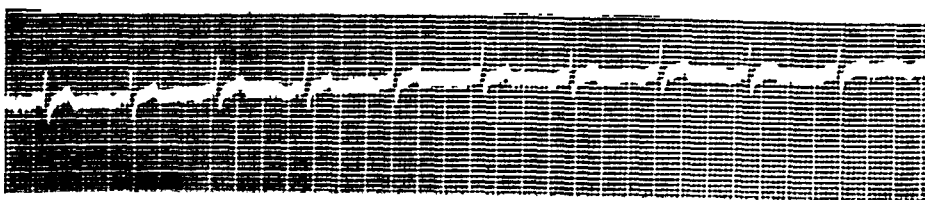
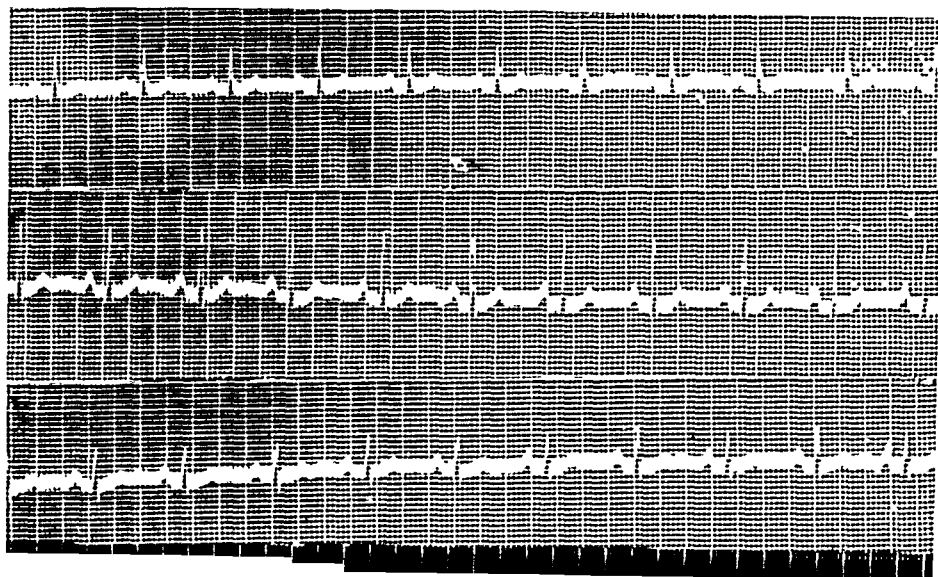


FIG. 5. Electrocardiogram taken after recovery from the acute cardiac illness

The patient was then started on forced feedings of a high caloric diet. He was also given 50 to 60 mg. of thiamine and 4 oz. of Brewer's yeast daily. Fluids were not restricted. On this regimen the patient improved rapidly. The mental symptoms cleared somewhat, the orthopnea and cyanosis disappeared, the dyspnea decreased and his appetite became better. His temperature dropped, the pulse rate decreased to 90. The heart decreased in size and, eighteen days later, measured 13 cm. in transverse diameter (figure 4). The venous pressure was now 15 cm., the magnesium sulfate circulation time (arm to tongue) was eleven seconds and the vital capacity gradually increased to 1,825 cc. The electrocardiogram now showed only a moderate tachycardia (figure 5). The blood pressure was 128/64. The chest sounded clearer and drier and serial roentgenograms showed clearing of the lung fields.

For about three months after the acute episode the patient's condition remained fairly stationary except for some improvement in the neuritic symptoms, that is, lessening of pain and paresthesias. He then failed rapidly and died.

*Necropsy* (Dr. S. Sanes) showed an extensive fibrocaseous tuberculosis of both lungs with cavitation in the upper lobe of the right lung and a bronchogenic spread throughout the remainder of the right lung. The heart weighed 250 g. and showed no evidence of myocardial or pericardial disease. There was a slight degree of atherosclerosis of the aortic valve and coronary vessels.

#### DISCUSSION

A bed-ridden tuberculous patient who had been eating poorly for months and who had a long-standing, mild, peripheral neuritis of the lower extremities with motor and sensory changes developed an acute cardiovascular syndrome. This was characterized by left ventricular failure (dyspnea, orthopnea, pulmonary congestion) and pronounced cardiac dilatation. There was no dependent edema or significant hepatomegaly. The venous pressure was only slightly elevated. The systolic arterial pressure remained within normal limits. The temperature and pulse rate were elevated and there was evidence of peripheral arteriolar dilatation with a warm flushed skin.

The low vital capacity can be correlated with the physical signs and roentgenographic evidence of advanced tuberculosis and pulmonary congestion. The electrocardiographic changes included sinus tachycardia and an altered S-T interval.

The velocity of blood flow (ether method) was normal in spite of the presence of congestive heart failure. This point aids in differentiating the cardiac failure of hyperthyroidism and beriberi from that occurring in other types of heart disease. In the latter, the circulatory rate is prolonged (3, 4). There was no response to the administration of digitalis, but after treatment with thiamine and yeast the patient rapidly improved. The orthopnea disappeared, the temperature and pulse rate dropped and the pulmonary congestion cleared as evidenced by physical examination, clearing of the lung fields on the roentgenogram and improvement in the vital capacity. The heart returned to normal size and the electrocardiographic changes disappeared.

The patient died of tuberculosis three months after recovery from the acute cardiovascular episode. The autopsy showed no evidence of disease of the heart or circulatory system which might have been responsible for the cardiovascular illness. In addition to the cardiovascular syndrome the patient had

clinical manifestations of multiple vitamin deficiencies, for example, polyneuritis and glossitis. This combination of vitamin deficiencies and severe circulatory dysfunction resembles occidental beriberi<sup>4</sup> (1, 2, 7, 8). In addition to the foregoing, the response to specific vitamin therapy leaves little doubt that the cardiovascular illness was a result of nutritive failure ("beriberi heart") in which a lack of thiamine played an etiological rôle.

#### SUMMARY

A bed-ridden tuberculous patient with a history of prolonged dietary insufficiency developed signs of left ventricular failure and pronounced cardiac enlargement. The patient also had a peripheral neuritis and glossitis. The administration of thiamine and yeast resulted in rapid clinical improvement and in a return to normal in the size and rate of the heart.

#### SUMARIO

Un tuberculoso encamado, con antecedentes de insuficiencia dietética prolongada, manifestó signos de insuficiencia del ventrículo izquierdo y pronunciada hipertrofia cardíaca. El enfermo también manifestaba neuritis periférica y glositis. La administración de tiamina y levadura obtuvo rápida mejoría clínica y normalización del tamaño y velocidad del corazón.

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<sup>4</sup> In oriental beriberi Wenckebach (5) has emphasized the occurrence of right ventricular dilatation but Keefer's (6) studies in China showed that this was not an essential feature of the "beriberi heart." That there is no rigid circulatory syndrome was noted by Weiss (2).

# ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS<sup>1</sup>

## XVI. Progressive Reinfection

### Part I

KORNEL TERPLAN

This paper records merely the anatomical findings in cases of postprimary pulmonary tuberculosis, with or without effects of intracanalicular spread to the trachea and larynx, to the pharynx and the gastro-intestinal tract. Just as in the following paper, dealing with various combination forms of chronic pulmonary tuberculosis and hematogenous involvement of different organ systems, including the lungs, the general morphological picture of these types is familiar to all acquainted with the pathology of tuberculosis. For this reason no detailed presentation of our material is intended. Table 1 gives, in comprehensive fashion, the pulmonary lesions brought about by exogenous reinfection or superinfection and additional changes caused by progression of this reinfection tuberculosis of the lungs. Again—as in the preceding paper—the relation of these lesions of pulmonary tuberculosis to the primary complex is of foremost interest. In addition, the more or less marked lymph node changes, apparently secondary to the progressive reinfection lesions, deserve a brief comment. This, we feel, is necessary, as it is not generally recognized that the bronchomediastinal lymph nodes and, for that matter, lymph nodes draining other organ systems like the mesenteric, peripancreatic, paraaortic and cervical groups, might show considerable involvement, with more or less diffuse caseation in progressive reinfection. Definite caseation of tracheobronchial lymph nodes, therefore, should not be used as an exclusive criterion of the so-called childhood type tuberculosis (as has been done by Wells (1) in examining pulmonary tuberculosis in Jamaican Negroes).

Some of the views on the nature of the so-called reinfection, as stated in the literature, have been discussed already in the preceding paper on *Restricted Pulmonary Reinfection*. The diversity of these views seems to justify the attempt to examine carefully the final morphological stages of pulmonary tuberculosis in their entire picture, complicated as it might be, especially in regard to their pathogenetic relation to the primary infection. It has been emphasized by Ranke (2) that tuberculous involvement of the bronchomediastinal lymph nodes is the less conspicuous the more the tuberculous process has expanded throughout the lungs via bronchi. Huebschmann (3), too, considered marked caseation of lymph nodes in connection with chronic tuberculosis of different organ systems, apparently including among these chronic pulmonary tuberculosis, a rare exception. Schuermann (4), however, has shown that there are always lymph node changes secondary to extensive postprimary tuberculous lesions, regardless of the pathways by which they were brought about—by the bronchi or by the blood-stream.

<sup>1</sup> From the Department of Pathology, Medical School, University of Buffalo, and the Pathology Laboratories of the General Hospital and Children's Hospital, Buffalo, New York.

TABLE 1  
*Anatomical findings in 18 cases of exogenous progressive pulmonary reinfection*

CASE NUMBER	AGE	RACE AND SEX	STATE AND SITE OF PRIMARY COMPLEX	LOCATION, ANATOMICAL TYPE AND EXTENT OF THE REINFECTION LESIONS	VARIOUS ADDITIONAL OR SPECIAL FINDINGS
2133	47	White F	Single, primary focus, pinhead-sized, calcified and ossified; base right lower, with hyaline-fibrous tubercles in regional lower and upper tracheobronchial lymph nodes	Fairly massive in basal portions of left lower with acute peribronchial tuberculosis throughout this lobe and with caseated pleuritis, in part in organization. No lymph node changes on the left side. Active tuberculosis in most of the bronchi in left lower lobe. Apices free	No hematogenous tubercles
E-34	53	Colored M	A few stony disintegrating foci in cherry-sized area; lower part right lower, with calcification in a few regional bronchopulmonary and lower tracheobronchial lymph nodes	Peach-sized, recent tuberculous cavity in lateral upper subapical field, right upper lobe. Intrabronchial spread to most of right upper, especially medial to and below cavity. Ulcerative tuberculosis right major bronchus and lower trachea with considerable dilatation. Small atelectatic scar in left apex	Intestinal tract free. No hematogenous seeding. No recent tuberculosis in lymph nodes regional to right upper. (No histological control.) Death from local corrosion of pulmonary artery in cavity
5299	69	White M	Single stony, ossified focus, lentil-sized; upper third right upper, with calcified regional bronchopulmonary lymph nodes	Entire upper third left upper in chronic chalky-calcified state, combined with extensive caseation, including a few hazelnut-sized cavities filled with chalky detritus. Recent peribronchial caseation in central and basal portions, left lower. Minimal ossification in apex of right upper	No active tuberculosis in right lung. No recent lymphogenous spread. Hemorrhages around recent peribronchitic caseated tubercles in left lower
4998	71	White M	Two firmly calcified complexes, hilar area, each side (foci obscured)	Incidental finding of extensive progressive ulcerative and caseated lesions with cavities in both lungs; in the right subapical area, fibrous, calcified scattered tubercles. Grossly no lymphogenous progression. (No histological control)	No hematogenous tubercles
3767	61	White M	Minute calcified focus above hilar level right upper, and firmly stony bronchopulmonary and upper tracheobronchial lymph nodes	Fibrocaceous, nodular tuberculosis extending over all lobes, most marked in left upper. Massive lymphogenous progression, including interlobar, lower and upper tracheobronchial and anterior mediastinal lymph nodes on both sides	No hematogenous spread. (Clinical diagnosis: Hodgkin's disease)
4621	61	White M	Two stony ossified foci, 2 and 4 mm. in diameter; apex and base, right lower. Firm stony changes in regional bronchopulmonary and lower tracheobronchial lymph nodes	Fibrocaceous tuberculosis of entire right subapical area extending into apex and several bronchi draining this area, with a few small chalky and many recent tubercles; several recent cavities with hemorrhages in wall. Massive caseated tuberculosis of regional upper tracheobronchial lymph nodes	Firmly caseated, partly fibrous-chalky subpleural lymph node in right middle lobe close to the hilum

5072	45	White F	Single pea-sized focus in firm stony ossified stato in right middle, and stony conglomerate tubercles in the regional bronchopulmonary and lower tracheobronchial group	Massive caseated pneumonia right upper third in area 4 to 5 cm. diameter, bulging toward mediastinal pleura with central cavitation 1 x 0.5 cm. Localized peribronchial tuberculosis in lateral and basal area right upper and in midportion of left lower, with recent caseation and massive recent tuberculous pneumonia with hemorrhages in left upper, middle and lateral field. Recent caseated tuberculosis in several lymph nodes regional to right upper, extending to right lower tracheobronchial group	No tuberculous changes in the interlobar and bronchopulmonary lymph nodes regional to the left lung
2570	40	White M	Primary focus, ossified, right lower. Minimal stony changes in regional bronchopulmonary lymph nodes	Extensive fibrocaceous tuberculosis with small cavities throughout left upper. Extending to lower part of right lung. Typical peribronchial arrangement. Caseated tubercles in the interlobar and a few bronchopulmonary lymph nodes on left side	Intestine negative. No hematogenous tubercles
2486	28	White M	Firm calcification of one mesenteric lymph node	Caseated, ulcerative progressive tuberculosis with several cavities, most marked apical and subapical left upper, extending to right upper and both lower lobes, especially left, with recent caseated lobular pneumonia. Moderate lymphogenous progression to lower and upper tracheobronchial and anterior mediastinal lymph nodes on both sides	Extension to larynx. A few scattered tubercles in liver, spleen and right kidney
3343	38	Colored F	Firm stony complex; primary focus lentil-sized; right lower. Firm calcification of regional intrapulmonary and bronchopulmonary lymph nodes	Several plum-sized cavities; medium third right upper and lower third left upper. Intrabronchial spread right upper and scattered in right middle and left upper. Moderate lymphogenous progression to right upper tracheobronchial lymph nodes (tuberculous hyperplasia)	A few ulcers and conglomerate tubercles in ileocecal area. No hematogenous tubercles
2320	52	White F	Firmly calcified; focus obscured, in upper third of left upper. Small calcified tubercles in regional left bronchopulmonary lymph nodes	Many calcified and fibrous cheesy lesions throughout both upper lobes, apical and subapical area with large cavity; left upper. Caseated peribronchial tuberculosis in lower part left upper and upper part left lower. Grossly no lymphogenous progression	Extensive ulcerative tuberculosis of intestine with isolated peritoneal tubercles
4038	20	Colored F	Single pinhead-sized stony focus; lower part right upper with stony tubercles in the right bronchopulmonary, upper tracheobronchial and paratracheal lymph node groups	Caseated lobular pneumonia in peribronchial arrangement in the two lower thirds of right upper and upper third of right lower. Additional peribronchial tubercles in base of right lower and scattered over the left lung. Fibrocaceous lesions in right interlobar and a few right paratracheal lymph nodes	Ulcerative tuberculosis of ileocecal area with massive caseation of mesenteric and periaortic lymph nodes. (Culture: human type)



TABLE 1—Continued

CASE NUMBER	AGE	RACE AND SEX	STATE AND SITE OF PRIMARY COMPLEX	LOCATION, ANATOMICAL TYPE AND EXTENT OF THE REINFECTION LESIONS	VARIOUS ADDITIONAL OR SPECIAL FINDINGS
5315	73	Colored M	Two firm stony complexes, right lower and left lower, to each a stony ossified focus, about hazelnut-sized, split up in many fragments. Massive stone formation in left bronchopulmonary lymph nodes and in two nodes of the right pulmonary ligament	Cavities from pea- to walnut-size; apical and subapical areas, most marked in left upper. Cavities in right apex, smooth-walled. Cavities in open communication with several bronchi. Caseated pneumonia entire lower half left upper and lateral parts left lower, and nodular peribronchial tuberculosis in all lobes of right lung. Massive caseation of all lymph nodes regional to the left lung and in both venous angles. Smaller caseated tubercles in lymph nodes regional to right lung	Tuberculous ulcers in larynx, trachea, left tonsil. Caseation of cervical lymph nodes. Tuberculosis of stomach and extensive ulceration of small intestine and ascending colon. Massive caseation of peritoneum, omentum and mesenteric lymph nodes with considerable serous exudate. Few miliary tubercles in liver, spleen and kidneys
2270	64	White M	Primary complex obscured. Minute calcified tubercles in right upper. Calcified chalky tuberculosis of bronchopulmonary lymph nodes at hilum of right upper	Unusually marked cavitations in both upper lobes with considerable shrinkage of the right upper and extensive intrabronchial spread, fibrocaseous to all lobes. Distinct microscopic lymphogenous progression to bronchopulmonary nodes at hila of both lungs	Several tuberculous ulcers in intestine. Caseated tuberculosis of mesentery; a few tubercles in liver
3379	31	White F	Single, firmly calcified focus, right lower. Extensive calcification of regional bronchopulmonary and lower tracheobronchial lymph nodes	Multiple chalky-calcified tubercles in right apical and subapical area with a few fibrocaseous tubercles and two small cavities. Several cavities (from 4 to 8 cm. in diameter) in entire left upper. Nodular peribronchial tuberculosis, remainder of left upper and left lower. Marked lymphogenous progression to all bronchomediastinal lymph nodes draining both lungs, most marked on the left side	Extensive ulcerative intestinal tuberculosis with perforated tuberculous appendicitis and lymphogenous progression through mesenteric, pancreatic and periaortic lymph nodes. No hematogenous tubercles. Cervical supraclavicular and axillary lymph nodes also caseated
4140	30	White F	Three minute calcified lesions, lower lateral part right upper. Firm adhesions around entire right lung. Regional lymph nodes negative on X-ray and gross dissection; microscopic hyaline tubercles in one regional interlobar node	Two cherry-sized recent cavities, one in lower lateral part of right upper, the other in left subapical lateral field. Massive tuberculous pneumonia (lobar type) of right upper and most of right lower and of left upper; scattered peribronchial tubercles in left lower and right middle. Recent conglomerate tubercles in both lower and upper tracheobronchial lymph nodes	Few recent ulcers in lowest ileum and cecum. Note: lobar type of recent tuberculous pneumonia (shortly following pregnancy). No hematogenous tubercles
4179	63	White M	Single, pea-sized, firmly calcified focus, right lower, with firm calcification of regional bronchopulmonary and lower tracheobronchial lymph nodes. (Focal calcification of pleura of right lower)	A few fibrocalcific nodules, right subapical area, and several cavities in both subapical areas. Progressive intrabronchial extension to both lungs with recent tuberculous, in part gelatinous bronchopneumonia in all lobes. Microscopically: conglomerate tubercles with caseation in regional lower tracheobronchial lymph nodes	Extensive ulcerative intestinal tuberculosis with perforation of ileum, progressing to mesenteric lymph nodes

5480	63	White M	Chalky-calcific, fibrous, with hazelnut-sized primary focus, base right lower. Extensive chalky-fibrous tuberculosis of regional bronchopulmonary lymph nodes crossing to right upper tracheobronchial group	Extensive older cavitation throughout left upper and more recent intrabronchial spread to left lower and entire right lung. Recent tuberculosis in the regional bronchomediastinal lymph nodes on both sides	Extensive chronic ulcerative tuberculosis of trachea, larynx and colon. A few hyaline tubercles in spleen
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In 14 per cent of the postmortem material studied by Schuermann, the caseation of bronchomediastinal lymph nodes regional to the lung tissue with marked progressive lesions was diffuse; in 86 per cent there were isolated or confluent tubercles without gross caseation. Koch and Puhl (5) have observed marked caseation of bronchomediastinal lymph nodes in cases with exudative cheesy pneumonia in the later stages of phthisis. Reichle and Gallavan (6) found, in 16 cases of adult type tuberculosis out of a total of 75, massive lymph node necrosis, and in 14 additional cases grossly noticeable conglomerate tubercles; in the remaining 45 cases, however, there were no tuberculous lesions in the bronchomediastinal lymph nodes regional to the various parts of both lungs harboring active tuberculous lesions. In these cases, in the words of Reichle and Gallavan, there was "complete lymphatic blockade."

We have selected for the present discussion 18 cases altogether. Of 5 of these the major gross and histological findings will be given with representative photographs of the diagnostic features of the primary complex and of some of the reinfection lesions.

#### CASE REPORTS

*Case 1:* (B. G. H. 4938) Twenty year old colored female. Cause of death: tuberculosis of the lungs and the intestine. (Plate 1<sup>2</sup>)

There is an old, stony primary complex with a pinhead-sized, typical primary focus in the lower lateral part of the right upper lobe and very firm stony changes in several lymph nodes of the regional bronchopulmonary, upper tracheobronchial and paratracheal groups (see X-ray photograph, plate 1). The postprimary lesions are presented by a massive, caseated bronchopneumonic process, involving fairly completely the lower two-thirds of the right upper lobe and the adjoining parts of the right lower lobe along the interlobar fissure. These changes show, especially along the periphery, a typical peribronchial arrangement. There are also a few smaller peribronchial tubercles in the basal portions of the right lower lobe and a few pinhead to small pea-sized recent peribronchial tubercles scattered over the left lung. There is localized caseation in an interlobar bronchopulmonary node between right upper and lower lobe. A few small fibrocaseous tubercles are also present in the right paratracheal lymph nodes, together with the firm stony remnants of the primary complex.

There is, in addition, very extensive ulcerative tuberculosis of the ileocecal valve and of the cecum, with superficial scarring of the mucosa and with massive caseation and small cavity formation in all mesenteric lymph nodes. The mucosa of the cecum is for the most part replaced by a tuberculous ulcer 6 cm. in width and 11 cm. in circumference, with atrophic scarring near the distal border and considerable papillary hypertrophy of the mucosa between the scars. There are many recent erosions and superficial ulcerations throughout this area. The entire small intestine proximal to the valve, and the entire colon distal to the ulcer are free of tuberculosis. The mesenteric lymph nodes are from hazelnut to cherry size and almost every single node contains a small lentil to pea-sized cavitation. The lymphogenous extension from the tuberculous cecum includes the lymph nodes around the celiac axis, the periaortic nodes at and below the level of the renal veins

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<sup>2</sup>The microphotographs are, in general, low magnifications (between 2 and 7X). They are consistent in each case except for some microphotographs of higher power showing histological details.

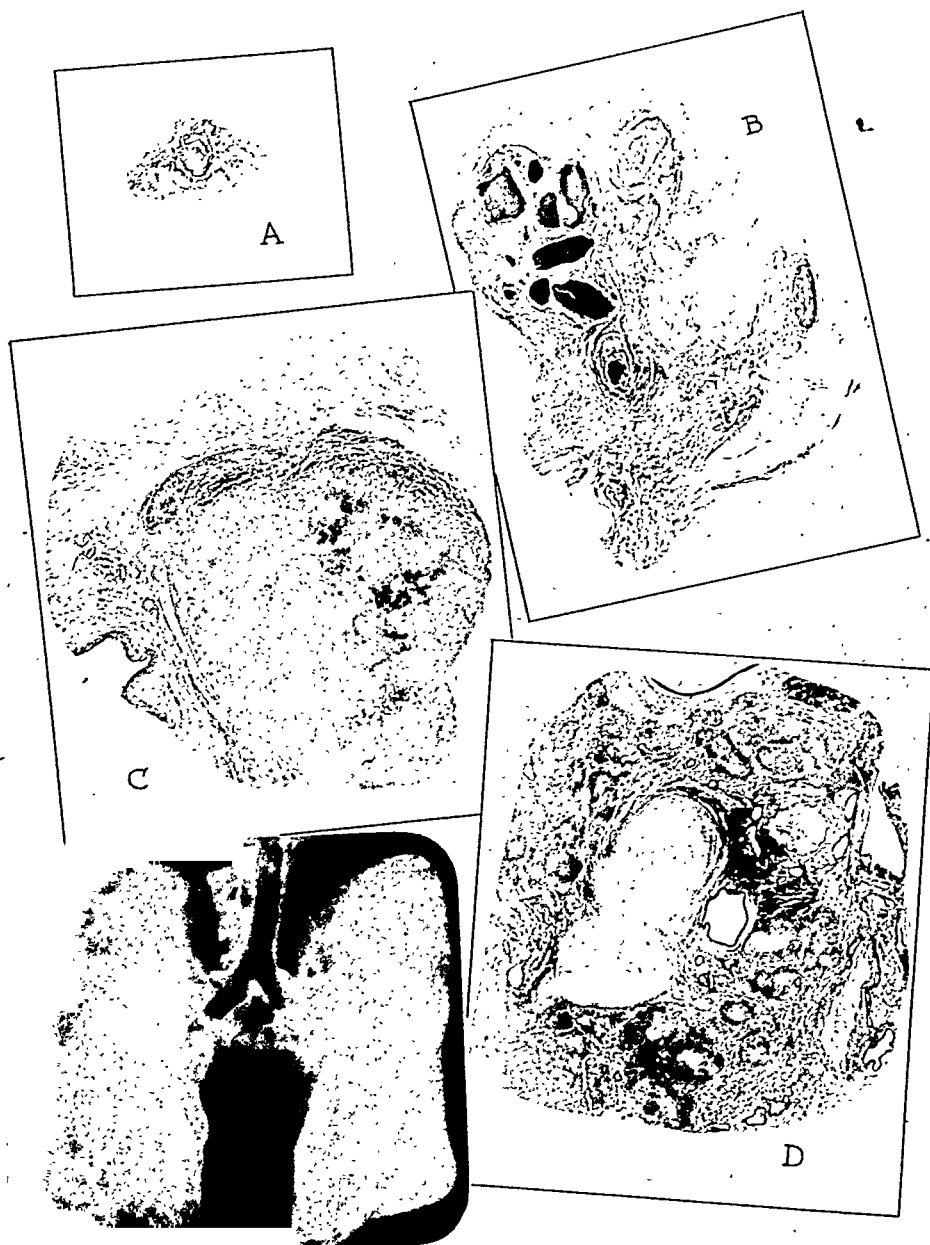


PLATE 1

and the iliac lymph nodes. A culture from the mesenteric lymph nodes revealed an abundant growth of colonies of the human type of tubercle bacilli. Plate 1 shows primary and reinfection lesions of the lung with the accompanying lymph node changes. In several lymph nodes, including the grossly caseated interlobar lymph node and especially the paratracheal group, the distinction between the old stony and the recent caseated tubercles is very clear. There is no merging of the latter with the former.

We see further the typical obsolete small primary focus (A) surrounded by a relatively thin hyaline-fibrous wall attached to a small branch of the pulmonary artery. The histological picture of the regional lymph nodes is very typical of obsolete stony conglomerate tubercles separated by thick bands of hyalinized connective tissue (B). There is also a recent conglomerate tubercle with diffuse caseation and moderate hyalinization of its wall in the same node. Several sections taken through the lower part of the right upper and the adjoining portion of the right lower lobe near the interlobar fissure show uniformly the same picture of caseated bronchopneumonia with typical recent peribronchial, lobular (acinous) spread. There is minimal liquefaction in the centre of the larger caseated lesions involving small bronchi and the peribronchial areas. This early disintegration of the central area is clearly seen in the photograph (D). The regional lymph node shows diffuse, caseated tuberculosis with slight fibrosis (C). The histological picture of the tuberculous lesions found in the base of the right lower lobe and in several scattered areas of the left lung is similar to that in the right upper lobe, except for the smaller calibre of the bronchi involved, forming the centre of these typical peribronchitic lesions.

This case, we believe, presents very typical findings of exogenous reinfection or superinfection with the most marked lesions in the lower two-thirds, including the infraclavicular field of the right upper lobe. Most probably there was a simultaneous infection of the ileocecal valve and the cecum. The progression from the intestine to the mesenteric and periaortic lymph nodes was much more marked than the corresponding lymph node lesions in the right interlobar and paratracheal groups draining the right upper and adjoining portions of the right lower lobe. There was no evidence of hematogenous tuberculosis, either from the old complex or from the reinfection. The absence of hematogenous tubercles in spleen, liver and kidneys and of miliary tubercles in the lungs was rather remarkable in this case with active lymphogenous spread throughout the mesenteric and periaortic lymph nodes. Also, the apical portions of both upper lobes were entirely free. The scattered tubercles in the left lung had the gross appearance of typical recent peribronchitic lesions, apparently caused by aspiration from the massively caseated bronchopneumonic process in the right lung.

The available clinical notes from the patient's chart were as follows: Six months previous to death there was a distinct fever lasting for three months; the temperature was usually normal in the morning and between 101° and 102° F. in the evening. The origin of this fever was not known. Four weeks before the patient died she was seized with diarrhea, nausea and emesis, and right lower quadrant pain. Her symptoms on admission pointed to a constricting ileocecal tumor. At laparotomy two days previous to death the diagnosis of tuberculosis was made for the first time, from a biopsy of a mesenteric lymph node which was caseated. A roentgenogram made shortly after admission, about one week previous to death, showed the right hilar region somewhat dense; the findings were not interpreted as an active tuberculous lesion.

*Case 2:* (B. G. H. 5072) Forty-five year old white female. Cause of death: uremia with secondary contracted kidneys. (Only the findings relative to tuberculosis will be given.) (Plate 2)

There is a typical primary complex in firmly calcified state, with a pea-sized primary focus near the anterior mediastinal border of the right middle lobe and with distinct calcification in the following three lymph node groups: the right bronchopulmonary just above the hilum to the right middle lobe, the right lower tracheobronchial and the right upper tracheobronchial group partly in front of the trachea, anterior and slightly to the right of the bifurcation.

There is recent, caseated pneumonia involving in a rather massive fashion the upper third of the right upper lobe in an area of 4 to 5 cm. in diameter. The visceral pleura shows thin adhesion bands to the dome of the pleural cavity. The mediastinal surface of the right upper lobe is distinctly protruding, due to the caseated pneumonic infiltration. There is superficial depression of the apex just at the site of the adhesions, suggestive of minimal collapse-induration. On section this entire area shows typical and fairly firm, grayish yellow, caseated consolidation, with a recent cavitation about 1 x 0.5 cm. in its centre. Lateral and below this fairly well circumscribed pneumonic area there are only rare lentil-sized peribronchial tuberculous nodules with distinct hemorrhagic zones. The mediastinal surface of the upper lobe immediately above the major bronchus is adherent to a few upper tracheobronchial lymph nodes. In all lymph nodes at the hilum of the right lung, especially in the bronchopulmonary group around the bronchus draining the upper lobe and in those above and below the major bronchus, there are lentil-sized, caseated tubercles, and in some of them more diffuse caseation. The size of these lymph nodes is hardly increased. Just as in the former case, the old stony lesions, firmly calcified, appear distinctly separated from the recent, caseated, conglomerate tubercles in the same lymph node.

There is localized extension of the recent tuberculous process from the right upper lobe to the midportion of the left lower, forming a small hazelnut-sized, ill defined, caseated lesion surrounded by recent peribronchial tubercles. In the lateral and basal areas of the right upper lobe similar recent peribronchitic tubercles are seen. Finally, there is considerable recent, confluent, bronchopneumonic consolidation in the mid- and lateral portion of the upper half of the left upper lobe, betraying its specific nature by but few grayish, nodular structures. The lymph nodes draining the left lung do not show gross tuberculous lesions. Microscopically, however, in a few lymph nodes of the anterior mediastinum and of the lower paratracheal groups a few recent conglomerate tubercles with central necrosis are found.

The lesions composing the primary complex (D and C) and those of the reinfection (A and B) were examined histologically, particularly including all lymph node groups draining both lungs. The primary focus (D) is a typical stony lesion with well recognizable alveolar pneumonic pattern. It is surrounded by an almost complete bony shell including a few islands of bone marrow. The hyaline-fibrous capsule around this ossified shell is, in some parts, of considerable thickness. There is a localized stony satellite tubercle, possibly as an original part of the large focus from which it was separated by ingrowing anthracotic fibrous tissue and finally broken off. There is collapse-induration between the focus and the pleura (in the photograph, to the right of the contour of the primary focus). The tracheobronchial lymph nodes contain firm stones, in part surrounded by bone tissue, and, in addition, fairly large caseated conglomerate and a few small epithelioid cell tubercles. In some lymph nodes of the lower bronchopulmonary and tracheobronchial group there are only recent and quite extensive caseated changes with hemorrhages around the caseated conglomerations.

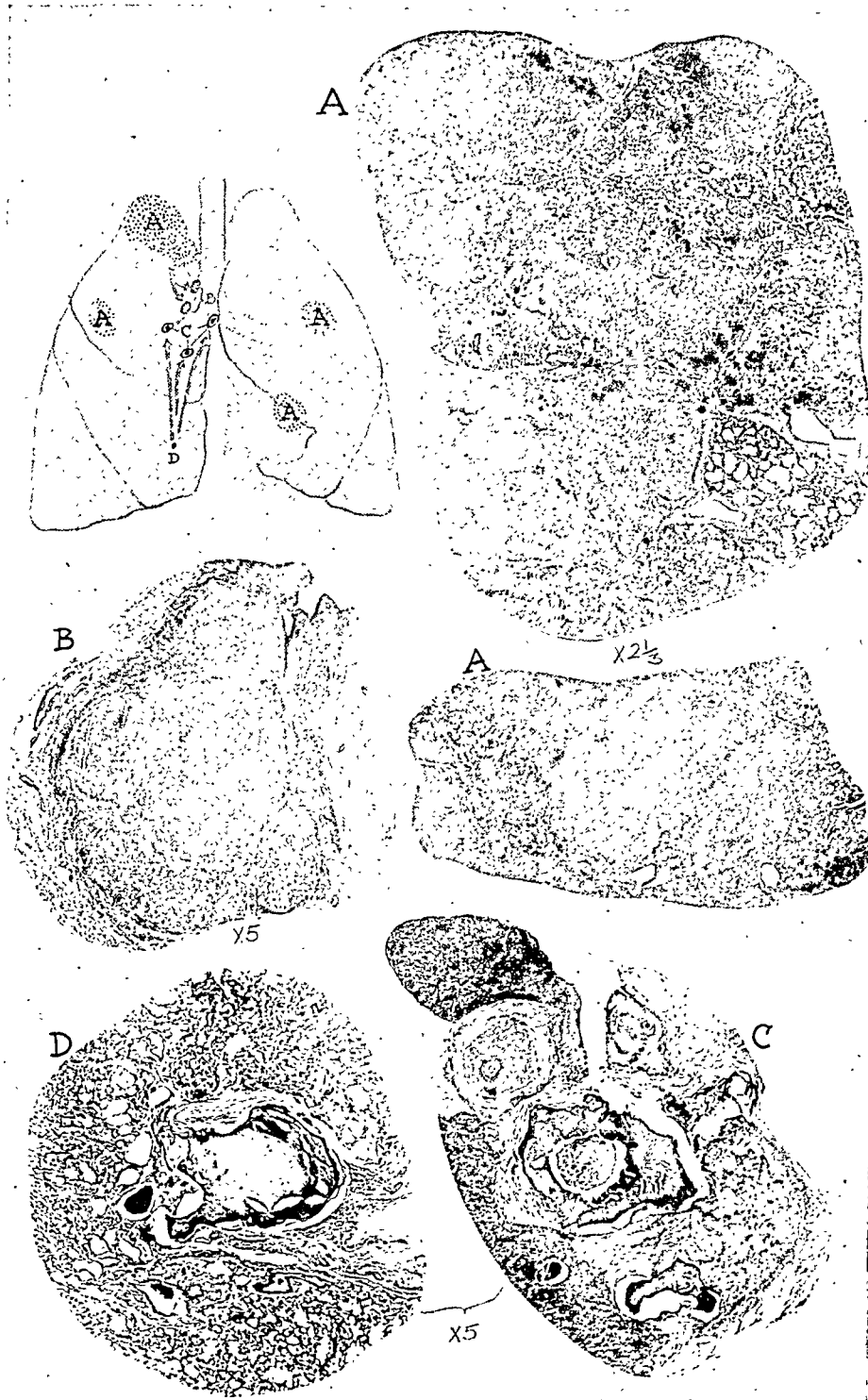


PLATE 2

The bronchopulmonary and the upper tracheobronchial lymph nodes regional to the primary focus show a similar picture with firm hyaline bands surrounding the calcified, stony matter, together with recently caseated tubercles rather close to the old stony lesions but distinctly separated from them (C).

Sections taken through the large reinfection lesions in the right upper lobe show a classical picture of caseated pneumonia with considerable accumulation of large mononuclear cells, as seen in the so-called large cellular tuberculous pneumonia. The massiveness of the caseation has, in some areas, an almost infarct-like appearance (A—upper). In several lobules there is recent disintegration of the caseated centre (A—lower). This was not suspected on gross examination. The upper bronchopulmonary and tracheobronchial lymph nodes draining the right upper lobe show large, conglomerate tubercles with diffuse caseation (B). They encroach rather closely upon the major bronchus without, however, penetrating its wall. Similar changes are seen in the right interlobar lymph nodes.

Sections taken from the left lung show a fairly firm, caseated tubercle in the centre of the left lower lobe, within typical lesions of recent tuberculous lobular pneumonia. There is, in addition, rather striking tuberculous peri- and endarteritis in a small branch of the pulmonary artery, in very close relation to the central caseation. The interlobar bronchopulmonary lymph nodes on the left side are free of tuberculosis. The paratracheal lymph nodes on both sides, however, show histologically distinct caseation. Apparently the tuberculous process had crossed from the right side to the left paratracheal group, as all lymph nodes at the hilum of the left lung and of the left interlobar group proved to be negative. Sections taken from the grossly more nonspecific appearing pneumonic portion of the left upper lobe show a picture of very recent tuberculous lobular pneumonia with but minimal central necrosis, and with a considerable amount of leucocytic, fibrinous and moderately hemorrhagic exudate. Finally, two minute calcified structures seen only in the X-ray photograph, one in each lower lobe—thought to be so-called osteoliths—proved to be typical phleboliths.

*Epicrisis:* We are dealing here with an entirely incidental finding of acutely spreading reinfection in a relatively recent state. The lymphogenous progression from the massive pneumonic area in the right upper lobe is not less marked than from any primary lesion. The primary focus and the large stony tubercles forming the primary complex appear grossly and especially histologically in a completely obsolete and healed state. Again, similar to case 1, there is no evidence of any hematogenous dissemination. There were neither old fibrous or calcified tubercles found anywhere outside the stony primary complex, nor recent tubercles in any organ which could have been reached only by the blood-stream.

*Case 3:* (B. G. H. 4140) Thirty year old white female. Cause of death: fulminating tuberculous pneumonia. (Plate 3)

The postmortem findings relative to tuberculosis included: three calcified foci, about 1 mm. in diameter, in the lower part of the right upper lobe near the lateral surface, and very firm adhesions of the entire right lung to the parietal pleura; distinct anthracosis and a few minute fibrous tubercles in the right interlobar bronchopulmonary nodes, but no calcified lesions in the regional groups, bronchopulmonary and tracheobronchial; a cherry-sized cavity in the subpleural area of the right upper lobe in its lateral basal portion with very distinct, recent caseated bronchitis and peribronchitic lesions extending towards the hilum; diffuse tuberculous pneumonia of the entire right lung of lobar type, resembling a late gray stage of a typical lobar pneumonia, with granular appearance of the alveolar



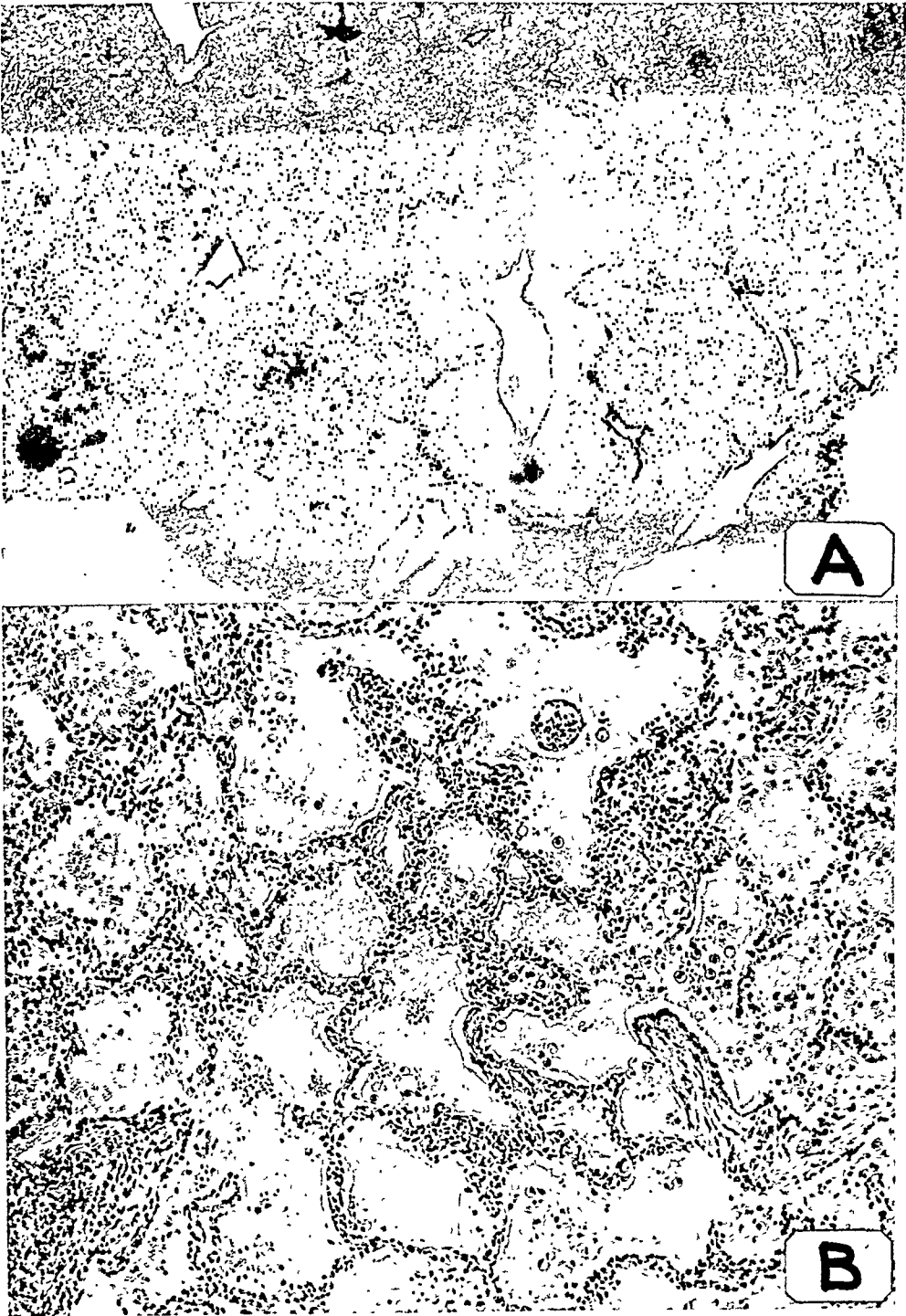


PLATE 3

exudate and prominent interlobular septae and with a few firmer, grayish white peribronchial areas, suggestive of recent tuberculous lobular pneumonia; complete firm fusion of all lobes of the right lung with each other and with the pericardial sac; a cherry-sized, recent caseated tissue sequester in the lateral part of the left upper lobe in the subapical area about in the middle third of the lobe, with beginning cavitation, and intrabronchial extension in the surrounding parenchyma, with typical caseated bronchitis and grayish white tuberculous peribronchitic lobular pneumonia with a few hazelnut-sized acinous lesions; tuberculous lobar pneumonia with marked inflammatory edema and the typical picture of gray hepatization in the remainder of the left upper lobe, except its uppermost and mediastinal portion; a few markedly hyperemic recent lobular pneumonic foci, apparently of tuberculous nature, in the central portion of the left lower lobe. The remainder of this lobe is well aerated. There is recent thrombosis of several intrapulmonary branches of the pulmonary artery, especially in the right lower and the left upper lobe; very distinct parenchymatous hemorrhages within and around some large tuberculous lobular pneumonic foci and some pleural suffusion; distinct edema and hyperemia of all bronchomediastinal lymph nodes on both sides and recent conglomerate tubercles in both lower and upper tracheobronchial groups; a few nickel-sized hemorrhagic tuberculous ulcers in the mucosa of the lowest portion of the ileum and in the cecum. No tubercles are found in the mesenteric lymph nodes. There were neither old nor recent tuberculous lesions in either apex.

In this case we are dealing with a very recent state of reinfection which had apparently involved first the lower lateral portion of the right upper lobe and the central infraclavicular area of the left upper lobe, in the presence of an obsolete primary complex with three minute subpleural tubercles in a firmly calcified state and only minute hyaline tubercles in one right interlobar bronchopulmonary lymph node. Before the cavities were discovered on cross sections, the gross picture of both lungs resembled lobar pneumonia in a gray and grayish-red state of hepatization. Smears from both cavities showed unusual masses of tubercle bacilli.

Histological sections through both cavities showed in their centre the lumen of a bronchus with the wall completely caseated, but with a few sequester-like, necrotic islands of cartilage remaining. Mucoid and leucocytic exudate, contained in the cavity, completely blends with the recently caseated wall which is infiltrated in some parts by large numbers of leucocytes. Due to contiguous caseation, the wall of this cavity appears unusually thick, in early state of coagulation necrosis (A). There is only minimal palisading of epithelioid cells along the outer border of the soft cavity wall. The surrounding tissue shows the typical picture of serous and, in part, large cellular pneumonia. The bronchi and bronchioli within the entire area surrounding the cavity show recent caseation. The protein-rich fluid exudate frequently appearing like edema, with a moderate number of typical large mononuclear cells, is the most impressive feature throughout the pulmonary tissue, especially in areas more remote from the cavity (B). Specific tuberculous changes are seen only along the border of the cavity, with a moderate number of typical Langhans' giant cells containing rather large numbers of nuclei. Otherwise the picture is, in many parts, nonspecific, showing focal caseation or an unusual abundance of large mononuclear cells and fluid exudate filling most of the alveoli. There were nowhere hematogenous tubercles, nor were there any fibrous scars in the pulmonary tissue surrounding either of the recent cavities.

Here, then, we are dealing with two entirely different episodes of tuberculous infection—far apart: an entirely obsolete one with a somewhat unusual type of primary focal lesions of very small size which apparently had led to diffuse pleuritis around the entire right lung. The “complex changes” of this primary infection were restricted to a few small hyalinized tubercles of miliary size in one interlobar node. This was followed—considerably later—by a new exogenous infection at a time at which all lesions, caused by the primary infection, had completely healed. There was no evidence of any reactivation around the firm small stony subpleural lesions, nor in the corresponding lymph nodes, only one of which had been originally affected to a minimal degree. No trace of any metastatic hematogenous lesion in connection with this old primary infection was found anywhere, neither in the lungs nor in other organs. The two cavitations had the structural appearance of very recent lesions; one of them, in particular, grossly very similar to a septic infarct with liquefaction necrosis. Serial sections were taken through both cavities and the surrounding lung tissue. There was nowhere any evidence of fibrosis or older caseated lesions in the lungs nor of apical scars.

The history in this case is of great interest: The patient, a thirty year old white married woman, was admitted on March 4, 1939. She had 2 children, aged twenty-two months and five months. Ever since the last delivery, with a normal postpartum convalescence, she felt weak and was moderately anemic. Four days previous to admission she was seized with a shaking chill, followed by emesis. Next day she had repeated chills with some mild hacking cough. On the day of admission she complained of slight pain along the ribs of the lower right chest. There was no rusty sputum. At the age of sixteen she had had pleurisy on the right side.

The clinical diagnosis on the basis of physical findings was lobar pneumonia, mainly in the right lower lobe. Type IV pneumococcus was found in the sputum. The pneumonic process gradually extended, involving the entire right lung. X-ray examination showed density over both lung fields, which was interpreted as pneumonia. The sputum was not examined for tubercle bacilli. The patient died on the 13th of March.

*Case 4:* (B. G. H. 4821) Sixty-one year old white male. Cause of death: lobar pneumonia. (Plate 4)

There are two primary lesions, one in the base, the other in the apex of the right lower lobe, with firmly encased stones in two lymph nodes of the bronchopulmonary group around the hilum of the right lower lobe. One of the primary lesions is slightly larger than the other. Both are, histologically, firm, stony structures, surrounded by a bony shell and anthracotic lung tissue. The regional lymph nodes contain firm stones broken up into smaller particles. The reinfection lesions are in the upper third of the right upper lobe, mostly in the subapical area but also extending into the lateral portion of the apex. There are a few minute, chalky-calcified lesions included in this area which, in the histological picture, proved to be silicotic nodules. Various sections taken through the entire subapical field show several distinct cavities with ragged walls, covered with necrotic debris, also a few older, firmly caseated and partly fibrous, oblong bronchiolar tubercles with considerable collapse-induration of the surrounding parenchyma. The tuberculous process around the cavities appears of a more recent, acinous, peribronchial, pneumonic type. Again, as

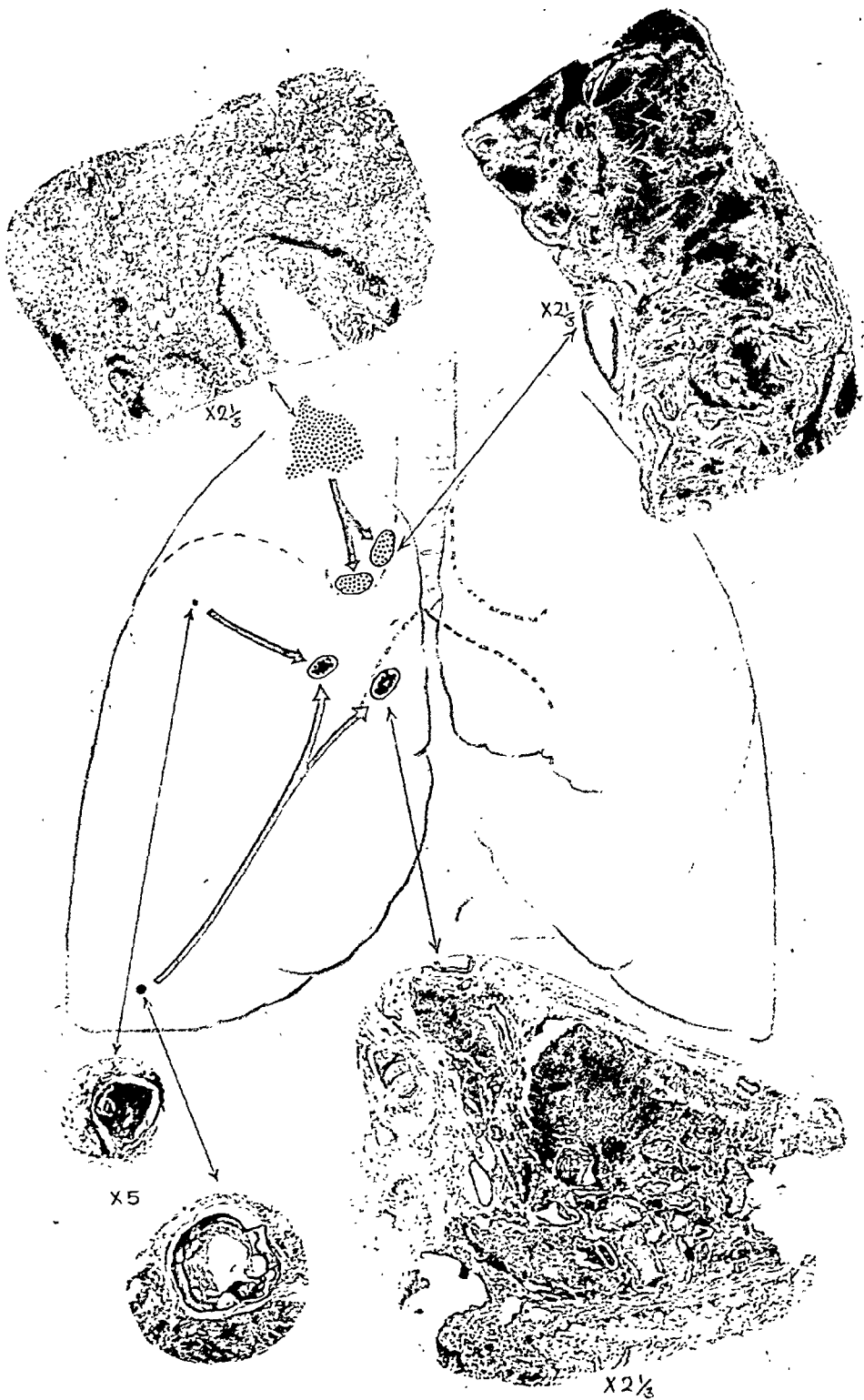


PLATE 4

in one of the former cases, there are distinct tuberculous endarteritic lesions with older fibrinoid necrosis in the wall and with eccentric narrowing of the lumen. In addition, there are, in the atelectatic areas, typical lesions of obliterating endarteritis in several small branches of the pulmonary artery. The ragged walls of the cavities are surrounded by recent capillary hemorrhages. The upper tracheobronchial lymph nodes and a few mediastinal lymph nodes above and anterior to the right major bronchus show considerable caseation. Almost the entire lymphoid structure is replaced by large, confluent conglomerate tubercles. A few smaller caseated tubercles were also present in the bronchopulmonary lymph nodes at the hilum of the right lower lobe, close to the old stony fragments. In some of the lymph nodes of the tracheobronchial group there are small central cavities in the huge caseated areas.

There is, in addition, a small hazelnut-sized, caseated nodule in the subpleural area in the right middle lobe. This was grossly first diagnosed as a typical reinfection focus, forming, with the bronchopulmonary and mediastinal lymph nodes, a second reinfection complex. Histological examination of this subpleural focus, however, reveals, especially in the elastic tissue stain, that it actually is a subpleural lymph nodule in massively caseated state. As there are no other tuberculous lesions in the right middle lobe nor in the right lower lobe, the caseated tuberculosis of this subpleural lymph node must be secondary to the extensive caseation of the bronchopulmonary and anterior mediastinal lymph nodes, possibly from retrograde lymphogenous spread.

There are neither old nor recent hematogenous tubercles secondary to the primary complex or to the reinfection lesions, in spite of the considerable recent lymphogenous progression. This case rather closely resembles the findings in reinfection complexes, as reported in previous papers (7), except that this reinfection lesion is of diffuse infiltrative and not of focal character. This reinfection lesion was an incidental postmortem finding. It was clinically not expected. A roentgenogram was not taken. The patient died from lobar pneumonia of the right lower lobe.

*Case 5:* (B. G. H. 5299) Sixty-nine year old white male. Cause of death: coronary sclerosis; status following prostatectomy. (Plate 5)

There is a typical calcified complex with one single old primary focus in the lateral part of the right upper lobe in its upper third, and very firm calcification of one regional bronchopulmonary lymph node. The histological picture shows a firm, old stone with clear alveolar pneumonic pattern, surrounded by a complete bony ring. The bronchopulmonary lymph node contains one large, stony conglomerate tubercle and, in addition, a few small hyaline, anthracotic nodules. Although their microscopic appearance, as seen in the photograph, is suggestive of firmly hyalinized tubercles, the final analysis makes it probable that these nodules are of anthracosilicotic nature. There are no recent tuberculous changes anywhere in this lymph node.

The extensive reinfection lesions in the entire upper third of the left upper lobe are in part in chalky-calcific, but mostly in active caseated state with a few cavities of hazelnut-size, filled with firm, caseated and chalky detritus. There are a few calcified branching structures, apparently casts of small bronchi. Throughout the base of the left lower lobe and along smaller bronchi in the central portions of this lobe there are the typical features of recent acinous bronchial and peribronchial tuberculosis with hemorrhages around the caseated peribronchitic tubercles. The right lung is free except for a localized calcified plaque in and underneath the pleura at the dome of the upper lobe.

The gross findings in the left upper lobe were interpreted as a chronic, recurring intra-bronchial tuberculosis in connection with an old reinfection, with signs of rather acute

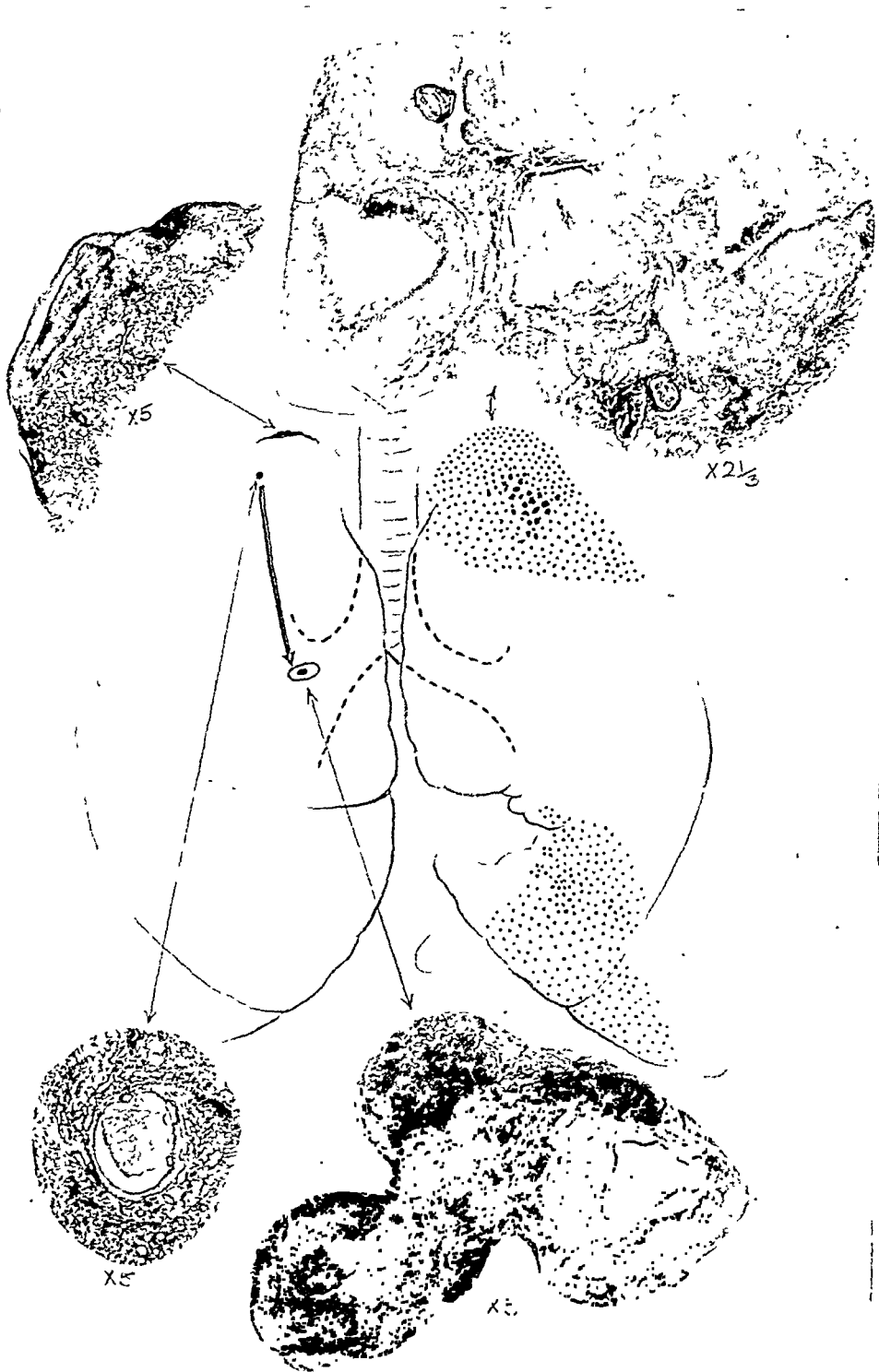


PLATE 5

intra-bronchial extension to the left lower lobe. Several sections taken from the left upper lobe show a typical combination of old chalky-calcified bronchial tuberculosis and more recent caseated and cheesy-fibrous lesions with several small cavities. A few old calcified tubercles filling out the lumen of smaller bronchi appear in an almost sequestered state (one of them is seen in the corresponding photograph on plate 5 in the lower field near the centre). Of special histological interest are small sequesters of partly calcified or completely ossified cartilage included within firmly hyalinized or old caseated tissue in the ragged walls of cavities. The location and peculiar shape of these fragments suggest that they represent the last remnants of the bronchial cartilage. Also noteworthy is localized persistence of bronchial epithelium in the wall of huge cavities, which are filled with caseated-chalky detritus, intermingled with tenacious mucoid secretion. The preserved though markedly inflamed mucosal lining shows hypertrophic papillary tuberculous bronchitis with marked proliferation of mucous glands within and underneath the swollen mucosa. Wherever larger bronchi are still recognizable there is considerable caseated tuberculosis within their wall. In several sections the gradual blending of the hypertrophic papillary bronchial epithelium with the firmly caseated wall and the caseated-chalky debris containing a great deal of mucoid secretion can be clearly observed. One is surprised to find in the centre of these large, solid, caseated bronchial tubercles with cavity-like disintegration a considerable amount of mucoid secretion. The uniformity of all these structures in cavities close by suggests that they all are part of, or communicate with, bronchial tubes, still capable of considerable mucoid secretion. The direct connection of the bronchi with the various cavities can be followed very clearly in the histological picture.

The changes in the left lower lobe are, microscopically, those of recent caseated bronchitis and peribronchitic lobular pneumonia. The scar in the right apex contains a firm stone within hyalinized tissue and shows distinct bone formation, consisting of thin trabeculae with anthracotic marrow. It is possible that this scar represents the final state of a very old superinfect; its structural age is certainly not different from the primary focus. The lymph nodes draining the left lung were not examined histologically in this case. There were neither gross lesions, nor was there any X-ray evidence of calcified or chalky changes. But it is possible that microscopic lesions of recent nature might have been present. There were neither old nor recent hematogenous tubercles in any organ. The entire analysis then, we feel, represents a fairly typical picture of an old exogenous reinfection or superinfection, restricted almost entirely to one lung and showing various phases of gradually extending intra-bronchial progression, including more recent changes of bronchial aspiration to basal portions of the left lung.

#### DISCUSSION

With the exception of 2 cases (no. 2320 and no. 2270, table 1), there was very clear evidence of an old obsolete primary pulmonary complex in all, and in one instance a stone formation in a mesenteric lymph node as the remnant of a primary intestinal tuberculosis. But even in the 2 exceptions there was distinct calcification of bronchopulmonary lymph nodes at the hilum of one upper lobe. Primary focus or foci, in these 2 cases, were entirely obscured by multiple older calcified or chalky tubercles in the apex or subapical areas tributary to the calcified-fibrous bronchopulmonary lymph nodes. This entire anatomical picture seemed to point to a very old superinfection. In one of our cases (no. 4140, table 1) the lymph node complex changes regional to three minute calcified sub-

pleural tubercles, covered by firm pleural adhesions, were only of microscopic size and of firm hyaline-fibrous character. Except for the old calcified-stony changes in the various lymph node groups or lymph nodes regional to the obsolete primary foci, there were no scars or old calcified tuberculous lesions seen outside of the lungs. In the last case of our series a few hyaline, small tubercles were found in the spleen. In this case the primary focus was of unusually large size and contained still a massive nucleus of chalky matter with cholesterol crystals within a very thick fibrous capsule. There were old and more recent caseated-fibrous tubercles in the bronchomediastinal lymph nodes. It is impossible to state whether these small hyaline tubercles, found only in the spleen, were metastases from the original primary complex or from the reinfection. Recent hematogenous dissemination from the postprimary lesions was seen in only 2 cases (no. 2486 and no. 5315), with but few miliary tubercles in liver, spleen and kidneys, apparently secondary to lymphogenous progression from the active reinfection lesions in the lungs. Especially in one of these cases (no. 5315), that of a seventy-three year old colored male, the tuberculous lesions in the bronchomediastinal lymph nodes were just as massive as those seen in progressive primary infections with diffuse caseation of the angulus lymph nodes.

The exogenous character of the reinfection lesions appears especially clear in our first 3 cases that were individually discussed. In these, in the presence of an entirely obsolete complex, relatively recent caseated pneumonic changes were found, restricted to the upper third of one upper lobe, with massive involvement of its subapical area. These cases represent, most probably, true reinfections. In some of the other cases with extensive older fibro-ulcerative or firmly calcified apical and subapical lesions (as in nos. 5299, 4998, 2320, 3379, 4179 and 5480) there is, we believe, no way to decide whether or not these exogenous infections were acquired before or after the primary complex had reached an obsolete, stony state. In all of them the subapical lesions, gradually progressing to the typical picture of chronic pulmonary tuberculosis, might have resulted either from superinfection or from reinfection.

As to the location of the reinfection lesions, they were unilateral in 4 instances only, in 2 cases in the right subapical field, in the other 2 in the upper third of the left upper lobe in one, and in the left lower lobe in the other. This latter observation is the only one in our series in which the location of the original reinfection or superinfection is outside of the upper lobes. Both apices and subapical fields remained entirely free in this case (no. 2133). In the remaining 14 cases, the reinfection lesions were present in both lungs. By comparative analysis of the gross findings in each lung, supplemented by histological studies, it seemed clearly evident that the reinfection had originally started in the right upper lobe in 4 cases (nos. 3343, 4938, 4998 and 5072), and in just as many in the left upper lobe (nos. 2486, 2570, 3767 and 5480). Especially in the few cases with relatively recent, massive pneumonic reinfections, the lesions in the contralateral lung were of distinctly secondary character, less massive in extent, and had the typical appearance of recent intrabronchial aspiration tubercles. In the remaining 6 cases, the reinfection lesions were fairly uniformly established in both lungs, especially

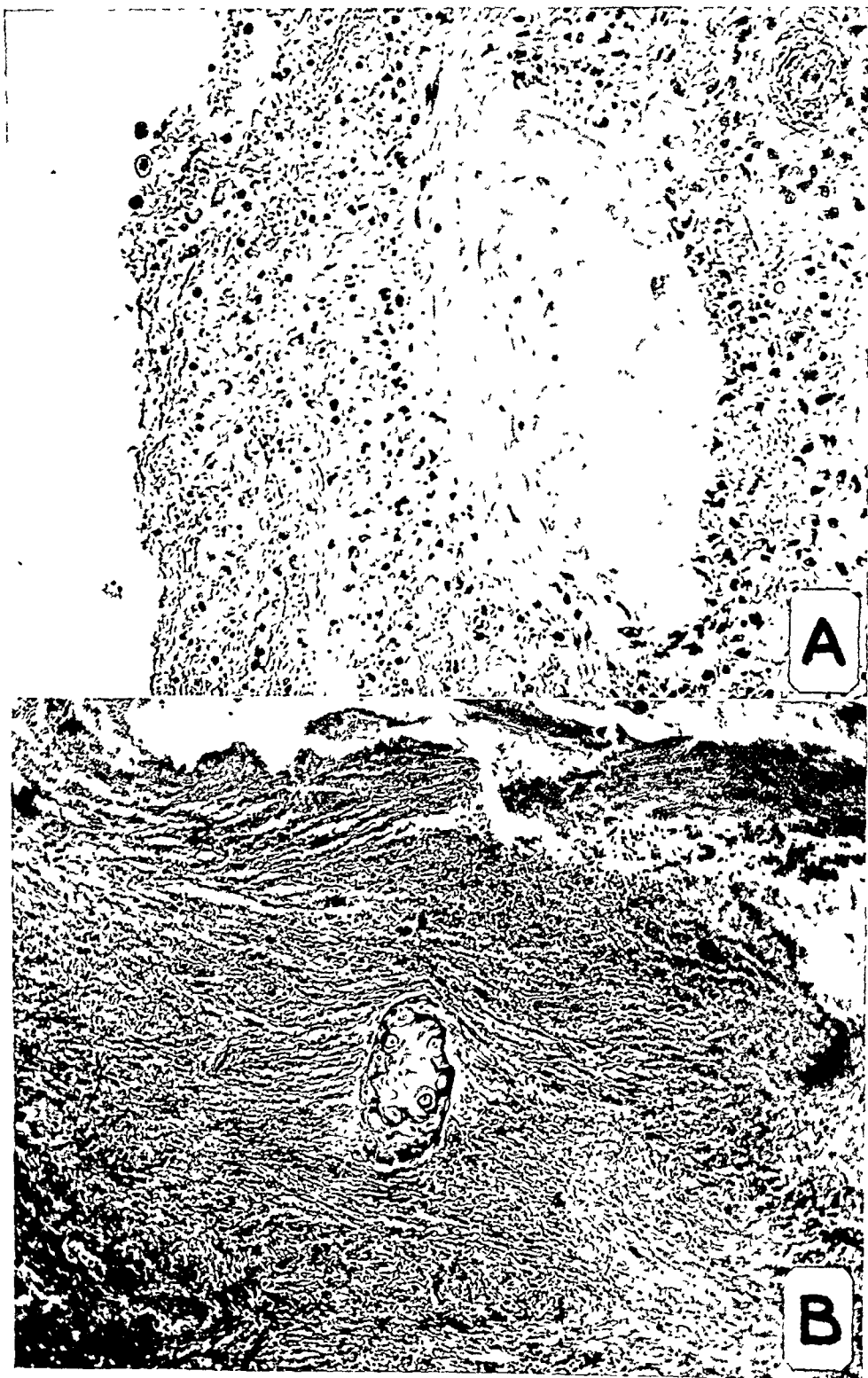


in both upper lobes. In most of these the chronic tuberculous lesions, including calcifications, fibrocased tubercles and cavities, appeared of fairly similar structure and extent in both upper lobes. It is these cases which showed the most marked degree of intrabronchial progression, in some instances of fulminating type, with massive gelatinous pneumonia and recent cavitations. Also, acute lymphogenous progression was uniformly present in the bronchomediastinal lymph nodes on both sides, secondary to the massively expanding pulmonic lesions. The age column in table 1 reveals that such massive intrabronchial extension, with considerable caseated pneumonic changes and recent liquefaction or extensive coagulation necrosis, occurred not only in younger individuals, around twenty and thirty years of age, but especially also in the older and pre-senile age groups.

As to the secondary lymphogenous tuberculosis in lymph nodes draining the areas with the active reinfection lesions, there was macroscopic evidence of this lymphogenous progression in 11 cases out of 18. In 7 of these it was described as massive or very marked, with diffuse or partial caseation; in 4 it was moderate. In 2 cases the tuberculous lesions in the bronchomediastinal lymph nodes were recognized only microscopically; in both there were small, caseated, conglomerate—and recent—epithelioid cell tubercles. In one case with the reinfection lesions restricted to the left lower lobe, combined with older caseated pleuritis around this lobe, there was neither gross nor microscopic evidence of tuberculosis in the lymph nodes regional to the left lower lobe. In the 4 remaining cases of our series the histological analysis of the bronchomediastinal lymph nodes regional to the various reinfection lesions was either incomplete or not carried out. There was no gross evidence of tuberculosis in the lymph nodes. It is possible, if not probable, that small, microscopic tubercles were present but missed. In a few cases in which the reinfection lesions were recent and restricted to one upper lobe the lymphogenous progression also was clearly restricted to the site of the original massive reinfection (no. 5072 and no. 4938).

Finally, in one of our cases with nodular, fibrocased tuberculosis, most marked in the left upper lobe, with the lesions in all lobes in typical peribronchial arrangement (no. 3767), the recent lymphogenous progression to the bronchomediastinal and tracheobronchial lymph nodes on both sides had led to such an extensive caseation and enlargement of these nodes that the clinical diagnosis, based especially on the roentgenological appearance of symmetrical mediastinal shadows, was Hodgkin's disease of the mediastinum.

It has been pointed out in the histological descriptions of the lesions in those lymph nodes in which old, obsolete stony tubercles were found, together with recent conglomerate caseated tubercles, that there was nowhere any morphological evidence that the recent lesions were directly contiguous to the old stony tubercles. In all sections it could be observed that the old tubercles were distinctly separated by hyaline bands from the recent tubercles, even if occasionally one of these seemed to encroach rather closely on the border or capsule of the old stony fragments. These pictures were only present in lymph nodes which were regional to the primary focus, as well as, at least in part, also to the areas harbor-



ing the recent active reinfection lesions. Although there were ample sources for lymphogenous infection of these lymph nodes from the recent reinfections, the histological picture in itself furnished good evidence that two entirely different episodes of infection were clearly marked, within the small confines of the bronchomediastinal lymph nodes, and that they were clearly separated. In analyzing lymph nodes containing tuberculous lesions of different structural age, the pathogenetic mechanism of endogenous exacerbation should be considered only in the absence of any active lesion in the tributary pulmonary parenchyma. I feel, for instance, that in a few cases interpreted as reactivation of the primary lesion by Reichle and Gallavan (8), in a paper on *Reactivation of the Primary Tuberculous Complex as a Source of Tuberculous Reinfection*, an exogenous reinfection cannot be excluded; that, in fact, it appears as the more likely cause for the recent tuberculosis in the lymph nodes which were regional to both primary focus and reinfection lesions. Only in the absence of any active process in the tributary lung, the findings of very old, less old and more recent active changes in the lymph nodes, in orthograde direction from and regional to the obsolete primary focus, can be interpreted in no other way but as a persistence of the original infection in the lymph nodes of the primary complex, causing this endogenous (lymphogenous) reactivation or exacerbation. Case 3 in the paper of Reichle and Gallavan, and also the last 2 cases (6 and 7) seem to conform to this type.

A few special histological features deserve a brief comment, as they are apt to be misinterpreted. These are the small remnants of bronchial cartilage found just like small bony, osteomyelitic sequesters, firmly encased within old fibrocaseous tissue, near the wall of old cavities (plate 6, B). When we saw these fragments for the first time in a case of chronic, fibrous, calcified subapical tuberculosis they were thought to represent ossified remnants of tubercles. They apparently persisted for a considerable time, undergoing calcification and ossification; but in the ossified state the original cartilaginous pattern is still present. These minute fragments show typical lacunar corrosion by firm, fibrous tissue along their contour. In another instance, with a very recent state of cavity formation and massive progressive caseation in and around a large bronchus, a small necrotic plate of bronchial cartilage was the only remnant of the bronchial tube (plate 6, A). It could be recognized with the usual staining methods and helped to identify clearly the bronchial wall as the site of the progressive cavity. It was found lying in sequester-like fashion, firmly impacted, within diffuse, uniformly coagulated necrotic and necrobiotic structures. There was no possibility with these staining methods to recognize any other layer of the bronchial wall.

In several of our cases of progressive pulmonary tuberculosis, various specific endarteritic processes of older and more recent nature could be observed, frequently with eccentric narrowing of the lumen (plate 7, A and B). Also, in one case, the last listed in our tables, with massive bilateral intrabronchial and lymphogenous progression, complicated by extensive cavitations and gelatinous pneumonia, there were a few cellular, noncaseating tubercles, filling out the lumen of smaller pulmonary veins. There was no evidence of hematogenous spread in this case, except for a few hyaline tubercles in the spleen. In all our cases

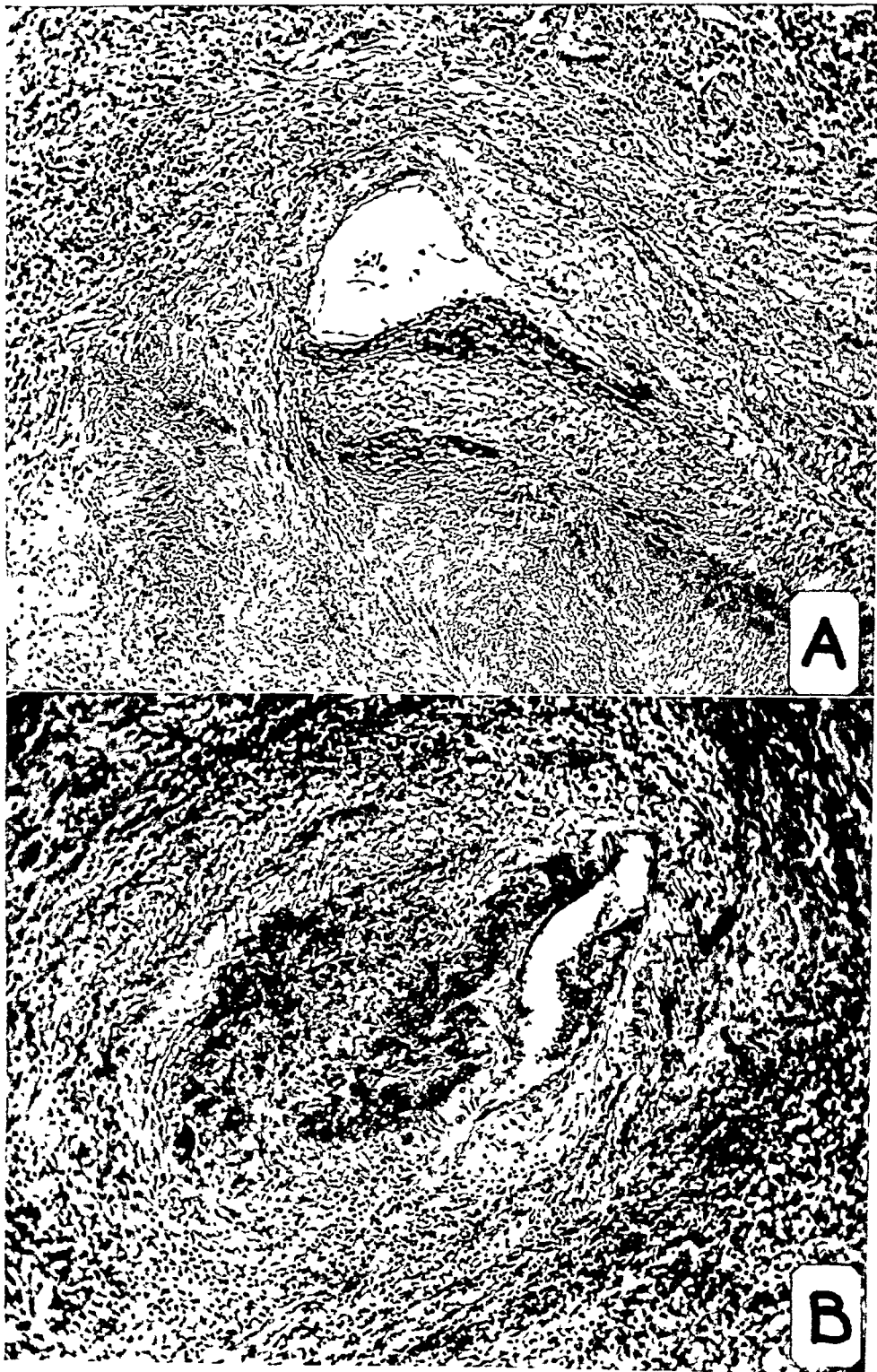


PLATE 7



PLATE 8

with most marked and acutely progressive tuberculous lesions with extensive caseation, these specific tuberculous inflammatory lesions of pulmonary arteries and veins were found in close topographic relation to the progressive tuberculous process. They were of entirely local character. There was no anatomical evidence that they had formed a source for hematogenous seeding. Finally, in 2 cases (no. 4821 and no. 5480), in areas of considerable collapse-induration, other pictures of obliterating endarteritis of smaller branches of the pulmonary artery could be seen (plate 8, A and B). In these the narrowing of the lumen was concentric in all arteries, caused by proliferation of the intima alone. This endarteritic process is not necessarily of tuberculous etiology, but rather a reactive change of the vessel wall, conditioned by the progressive collapse-induration, resulting in a permanent local strain on the pulmonary circulation. Note in photograph B the extreme reduction of the lumen—to pinpoint size—in the centre of a pulmonary arteriole. The original vascular nature of this nodular structure is hardly recognizable at first glance.

The organs or organ systems frequently involved in so-called open cases of pulmonary tuberculosis are major bronchi, trachea, larynx, pharynx and tonsils, and different parts of the gastro-intestinal tract, especially lower part of small intestine and colon. Among the 18 cases of our series there was very clear evidence of intracanalicular spread in 10. In one of them only the larynx was involved (no. 2486); in 2 others, larynx and trachea (no. 5315 and no. 5480). One of these (no. 5315), the case of a seventy-three year old colored male, showed most marked tuberculosis in different parts of the intestinal tract, with ulcerations in the stomach and small and large intestine. Omentum as well as all mesenteric lymph nodes were massively caseated. This unusual tuberculous lesion in the stomach was presented by an entirely blastoma-like infiltration and localized superficial ulcerations involving the midportion of the fundus, especially the so-called *Magenstrasse*, in an area of 8 x 7 cm. The wall of the stomach in this area of the tuberculous infiltration was 5 to 6 mm. thick. There was considerable papillary hypertrophic tuberculosis in the antrum of the pylorus, while the remainder of the fundus was entirely normal. The other important findings are listed in table 1.

The clinical history in this case reveals that only in the short time of four weeks prior to death, rather suddenly, the first subjective symptoms appeared which pointed to the stomach. The patient stated that he felt perfectly well until that time when his stomach began feeling full, even though he did not eat much. Soon he refused to take in any food. In spite of this a diarrhea set in. The abdomen became increasingly distended, bulging in both flanks; there was a definite fluid wave. A paracentesis yielded almost 3 liters of protein-rich fluid. The diagnosis of cirrhosis of the liver was seriously entertained, but the X-ray appearance of the chest was highly suggestive of progressive tuberculosis of the left lung.

In the remainder of these 10 cases (7 altogether) the ulcerative lesions were restricted to small and large intestine. In 2 of them the ultimate cause of death was diffuse peritonitis, following perforation of a tuberculous ulcer in the lower

ileum in one, and perforation of an ulcerated tuberculous appendix in the other. In all these cases with extensive ulcerations of the intestinal tract, there was very massive caseation in the mesenteric lymph nodes. Although in some of these cases lymphogenous progression had extended from the mesenteric to the periaortic lymph nodes, there were, only in one of them, a few miliary tubercles in liver, spleen and kidneys.

Brief abstracts of clinical histories of a few selected cases of our series which were not discussed individually will be added. The anatomical findings in these cases were those of a marked fibro-ulcerative caseated pulmonary process (phthisis), in some of them combined with intestinal tuberculosis. The discrepancy between the extensive anatomical lesions and the relatively short duration of symptoms pointing to progressive disease or the absence of subjective pulmonary symptoms in a few of these cases might perhaps surprise those who are not familiar with the large variety of patients seen frequently only in the final stages of their disease in a general hospital and who are sometimes not suspected of suffering from progressive tuberculosis. These brief notes should be read with the corresponding anatomical findings listed in table 1.

*No. 4998:* This patient, a white senile male, had suffered for several years from a cancer on the back (following roentgenological treatment of a skin lesion). He was, repeatedly, for several months a ward patient in the orthopedic service, where he was treated for a fracture of the neck of the femur. Tuberculosis was not suspected clinically.

*No. 3767:* The patient, a sixty-one year old white male, began to cough, with large amounts of sputum, two years previous to his admission to the hospital. He had night sweats and a feeling of weakness. There was no weight loss. A specialist advised bronchoscopy. The sputum was persistently negative for tubercle bacilli. Roentgenologically, broad mediastinal shadows were seen. They were interpreted as suspicious of Hodgkin's disease. X-ray treatment was given. When a dense area was seen later on the X-ray film between the third and sixth rib on the left side, it was interpreted as the effect of pulmonary congestion. It was clinically not known that this patient had tuberculosis.

*No. 3343:* A thirty-eight year old colored female had productive cough with shortness of breath for several years. There was considerable weight loss. She was a patient in the hospital only for the last eight days preceding her death. Roentgenologically there was mottling of both upper lobes and a small cavity was seen in the right upper. X-ray and physical findings were diagnostic of progressive pulmonary tuberculosis.

*No. 2486:* This patient, a twenty-eight year old white male, was a porter in dance halls and saloons. There was a history of "pneumonia" with pleurisy in three successive years, several years previously. During the last two years he coughed regularly in the mornings; once he spat up fresh blood. He was seen repeatedly in the out-patient department during the last five months previous to his death. The cervical lymph nodes were swollen; he had "cryptic tonsils" and complained of sore throat. Roentgenologically there was mottling in both upper lobes. Although this was felt to be the result of tuberculosis, it was stated that the occupation of the patient—he had to sweep dusty floors and dusty cellars for several years—might have played a part in causing these pulmonary densities

seen in the X-ray film. Obviously the specific lesion of the throat, found postmortem, was not expected in spite of the swollen cervical lymph nodes. A tonsillectomy was performed two months previous to death. Since that time his emaciation progressed rapidly. There was increasing soreness of the throat and almost complete inability to eat. The patient was finally admitted to the hospital in a rapidly failing state and died the day after.

*No. 2570:* The patient, a forty-nine year old white male diabetic, was admitted on February 22, 1934, and died on the 26th of March of the same year. Roentgenological examination showed density over the entire left chest. It was interpreted as a callous pleuritis. There were distinct physical findings over the left lung. A diagnosis of tuberculosis was not made. There were, however, a few skin lesions diagnosed clinically as papillary necrotic tuberculids. This was the only note suggestive of tuberculosis in the chart of the patient.

*No. 3379:* This patient, a thirty-one year old white female, gives the history of shortness of breath, palpitation and anginal type of pain for the last two months previous to death. In the last two weeks, diarrhea was persistent with gradual distention of the abdomen and considerable emesis. The lymph nodes on the left side of the neck were swollen seven years previously. There was no history of cough, but distinct weight loss. Gradually, several additional peripheral lymph nodes, especially the supraclavicular and the axillary groups, became distinctly enlarged. The examination at admission revealed distinct physical findings above the left apex. A biopsy taken from the left axilla on the day of admission, which was one day before the patient died, showed diffuse caseated tuberculosis. The patient was too ill for roentgenological examination. Apparently the reinfection is at least of seven years' duration in this case. Acute pulmonary symptoms, however, were not present until two to three months before the patient died.

*No. 2270:* The patient, a sixty-four year old white male, was operated for an appendiceal abscess six weeks previous to death. This abscess—as was found postmortem—had formed in connection with a covered perforation of a tuberculous ulcer of the cecum. The first complaints of vomiting and epigastric pain had pointed to the abdomen. The chest was found clear on physical examination at that time. Only three weeks previous to death, the lungs were examined roentgenologically and showed much mottling with cavity formation on both sides. This was diagnosed as active tuberculosis.

#### SUMMARY

The anatomical picture in 18 cases of "exogenous" progressive pulmonary reinfection tuberculosis is presented. Their ages range from twenty to seventy-three years, with the majority in the older and presenile age groups. In 15 of them there were the typical obsolete remnants of a primary pulmonary infection; in one a primary intestinal infection was present. In the remaining 2 cases, primary focus or foci were obscured among multiple apical and subapical calcified tubercles of apparently postprimary character; the hilar lymph nodes regional to these areas, however, were distinctly calcified, just as in any typical obsolete primary complex. Anatomical evidence of gradual intracanalicular spread involving trachea, larynx, pharynx, and/or gastro-intestinal tract was present in 10 cases of this series. The anatomical-histological analysis of the entire material



pointed in all cases to the exogenous nature of these postprimary reinfection lesions. They were found in typical subapical or apical location in 17, and in the left lower lobe in one case. In a few instances, discussed in some detail, the postprimary lesions were of relatively recent caseated pneumonic character, spreading in typical intra- and peribronchial fashion throughout the subapical area. This massive, though still somewhat restricted, pulmonary tuberculosis—in the presence of an entirely obsolete primary complex with no other lesions whatsoever, pulmonary or extrapulmonary, in connection with the healed primary infection—is considered the result of true “exogenous” reinfection. In other cases of this series in which some of the postprimary apical and subapical lesions had reached an advanced structural age, no decision can be made as to whether or not they were caused by superinfection or true reinfection.

Lymphogenous spread from the progressive postprimary reinfection lesions was pronounced in 10 cases out of 18; in some of them with massive caseation of the entire bronchomediastinal lymph node chain. In lymph nodes regional to both, old primary and less old progressive reinfection lesions, the stony remnants of the primary infection were distinctly separated by firm hyaline tissue from the more recent lymphogenous tubercles secondary to the reinfection lesions, found in the confines of the same node. Such pictures of old and recent tuberculous lesions, close together but not merging with each other, might be misinterpreted as endogenous exacerbation if it is not generally realized that lymphogenous spread from progressive reinfection lesions can lead to diffuse massive tuberculosis, with caseation of any lymph node group including the broncho-mediastinal. Hematogenous tubercles secondary to the spreading reinfection lesions were few and seen in only 2 cases of this series.

Among features of histological interest, attention is called to small sequester-like remnants of bronchial cartilage, calcified or ossified, found impacted within old fibrocaseated or hyalinized tissue, which might be mistaken for ossified tubercles, as the original bronchial wall is completely destroyed or obscured. Also—apart from tuberculous arteritis contiguous to progressive caseation—typical changes of concentric obliterating endarteritis seen in small branches of the pulmonary artery in areas of collapse-induration are described, and their probable pathogenesis conditioned by obturation atelectasis of the lung tissue which they supply is discussed.

Brief abstracts of some clinical histories are presented to demonstrate the discrepancy between the extensive anatomical lesions pointing to a chronic disease of long standing and the relatively short duration of subjective complaints or objective symptoms of the rapidly progressing, fatal disease. The material includes one instance of fulminating tuberculous pneumonia with acute symptoms lasting only thirteen days, and diagnosed as pneumococcus lobar pneumonia, and an unusual observation of blastoma-like tuberculous infiltration of the stomach, in an otherwise typical case of progressive cavernous phthisis with intracanicular spread to larynx, trachea, left tonsil and entire intestinal tract. In this case the first subjective symptoms pointed to the stomach and were not noticed until four weeks prior to death.

## SUMARIO

Preséntase el cuadro anatómico de 18 casos de tuberculosis pulmonar evolutiva "exógena" tipo reinfección, variando la edad de los enfermos de 20 a 73 años y correspondiendo la mayoría a los grupos de edad más avanzada y presenil. En 15 observáronse los típicos restos anticuados de una infección pulmonar primaria; en uno existía una infección intestinal primaria, mientras que en los otros dos el foco o focos primarios estaban enmascarados entre tubérculos calcificados, apicales y subapicales múltiples, de naturaleza aparentemente postprimaria, pero los ganglios linfáticos hiliares de esas zonas se hallaban netamente calcificados como en cualquier típico complejo primario anticuado. En 10 casos había signos anatómicos de propagación intracanalicular gradual que afectaba la tráquea, laringe, faringe y o el aparato gastrointestinal. El análisis anatómico-histológico de todo el material denotaba en todos los casos la naturaleza exógena de esas lesiones postprimarias tipo reinfección, habiéndose encontrado en típica situación subapical o apical en 17 casos y en el lóbulo inferior izquierdo en uno. En algunos, discutidos algo a fondo, las lesiones postprimarias fueron de naturaleza neumónica caseada relativamente reciente, propagándose en típica forma intra y peribronquial por toda la zona subapical. Esta tuberculosis pulmonar masiva, aunque todavía algo limitada,—en presencia de un complejo primario absolutamente anticuado, sin ninguna otra lesión pulmonar o extrapulmonar en relación con la infección primaria cicatrizada—se considera resultado de verdadera reinfección "exógena". En otros casos de esta serie en que algunas de las lesiones apicales y subapicales postprimarias habían alcanzado histológicamente una edad avanzada, no puede determinarse si fueron o no producidas por superinfección o verdadera reinfección.

La propagación linfógena de las lesiones postprimarias evolutivas de reinfección fué pronunciada en 10 de 18 casos, en algunos de ellos con caseación masiva de toda la cadena de ganglios linfáticos broncomediastínicos. En los ganglios linfáticos regionales, tanto en las lesiones primarias antiguas como evolutivas de reinfección menos antiguas, los restos pétreos de la infección primaria estaban netamente separados por tejido hialino masivo, de los tubérculos linfógenos más recientes secundarios a las lesiones de reinfección encontradas dentro de los confines del mismo ganglio. Esos cuadros de lesiones tuberculosas viejas y recientes, apiñadas, pero sin confundirse, podrían ser interpretados erróneamente como exacerbación endógena, de no comprenderse claramente que la propagación linfógena de lesiones evolutivas tipo reinfección puede conducir a tuberculosis masiva difusa, con caseación de cualquier grupo linfático, incluso el broncomediastínico. Los tubérculos hematógenos secundarios de las lesiones de reinfección en vías de propagación fueron pocos y sólo observados en dos casos de la serie.

Entre las características de interés histológico llaman la atención los restecillos parecidos a secuestros de cartílago bronquial, calcificados u osificados, que se encontraban incrustados en viejo tejido fibroc caseado o hialinizado, y que podían confundirse con tubérculos osificados por hallarse completamente destruída u

obsurecida la primitiva pared bronquial. Igualmente, aparte de la arteritis tuberculosa contigua a la caseación evolutiva, describense típicas alteraciones de endarteritis obliterante concéntrica observada en ramillas de la arteria pulmonar en zonas indurado-aplastadas y discútese su probable patogenia acondicionada por la atelectasia obturada del tejido pulmonar.

Preséntanse breves sumarios de algunas historias clínicas para demostrar la discrepancia que existe entre las lesiones anatómicas que denotan afección crónica de mucha duración y la duración relativamente breve de los síntomas subjetivos u objetivos que producen la afección letal y de rápida evolución. El material comprende un caso de neumonía tuberculosa fulminante y síntomas agudos que sólo duró 13 días, y diagnosticado como neumonía neumocócica, y una observación extraña de infiltración tuberculosa blastomídea del estómago en un caso, por lo demás típico, de tuberculosis cavernosa evolutiva con difusión intracanalicular a la laringe, tráquea, amígdala izquierda y todo el intestino. En este caso los primeros síntomas subjetivos apuntaban al estómago y no fueron advertidos sino cuatro semanas antes de la muerte.

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# ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS<sup>1</sup>

## XVII. Progressive Reinfection

### Part 2

KORNEL TERPLAN

This paper should be considered as the direct continuation of, or the second part to the preceding one. Both are concerned with anatomical results of exogenous reinfection. The preceding paper contained a selection of various forms and states of chronic pulmonary tuberculosis with or without anatomical evidence of further intracanalicular spread to the upper respiratory and the digestive tract. Although secondary lymphogenous progression was rather marked within this group, hematogenous seeding to various organs, including the lungs, was either absent or comparatively negligible. In the present paper, on the other hand, we are dealing with various combinations of chronic or acute tuberculous changes in different organ systems, particularly including the lungs, of clearly hematogenous character with typical exogenous pulmonary reinfection lesions. In most of the cases included in this paper the hematogenous lesions had either completely dominated the clinical course of the disease or had led to its fatal termination. Yet, in the final anatomical pictures, it seemed not difficult to differentiate between the older lesions of reinfection—typical in their morphological character and location, though varying in the individual cases in their extent within the lungs—and the more recent hematogenous pulmonary tubercles. Whenever such hematogenous miliary tubercles were present they were part of a more or less generalized miliary seeding. Our anatomical analysis seemed to indicate that the various hematogenous lesions were directly or indirectly related to the exogenous pulmonary reinfection. In addition, just as in the preceding paper, an old obsolete complex of primary infection was present in most if not in all of our cases, and no direct or indirect pathogenetic link could be found between the obsolete primary complex and the postprimary lesions of chronic pulmonary tuberculosis. These showed, just as in the cases presented in the previous paper, the same topographic location, anatomical character and intrabronchial type of progression which we have learned to interpret as the result of exogenous superinfection or reinfection. The pathogenesis of these various hematogenous lesions, then, which were found in combination with restricted or progressive, usually chronic, pulmonary tuberculosis is obviously different from the well known pictures of hematogenous tuberculosis observed in more or less direct connection with the primary infection. A comparison of the tables attached to this paper with those of the succeeding paper will show this difference clearly. In the succeeding paper we will deal with the well known condition of progressive primary tuberculosis in adults (similar to the so-called childhood type) and with

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TABLE 1  
*Anatomical findings in 13 cases of hematogenous tuberculosis secondary to exogenous reinfection*

CASE NUMBER	AGE	RACE AND SEX	STATE AND SITE OF PRIMARY COMPLEX	LOCATION, ANATOMICAL TYPE AND EXTENT OF THE REINFECTION LESIONS	HEMATOGENOUS LESIONS AND VARIOUS ADDITIONAL OR SPECIAL FINDINGS
2181	68	White M	Two stony-ossified complexes with three pinhead-sized foci, two in left lower and one in right lower. Firm calcification and partial ossification of the bronchopulmonary lymph nodes regional to both lower lobes and a few calcified and partly ossified subpleural lymph nodules in left lower	Old fibrous tuberculosis with a few small cavities in right subapical field and massive chronic fibrous tuberculosis in left subapical field. Lesions start 2 to 3 fingers below apex. Fibrous tuberculosis of right upper tracheobronchial and paratracheal lymph nodes. Massive intrabronchial spread to remainder of left upper and recent small scattered peribronchial tubercles in both lower and right middle	Cheesy tuberculosis of ninth and tenth dorsal vertebral bodies, with large paravertebral abscesses; compression of spinal cord. Many conglomerate tubercles in liver, some of them calcified. Miliary and conglomerate tubercles in kidneys, spleen, supraprenals; caseation of prostate. Older tuberculous ulcers in colon. Tuberculous hyperplasia of mesenteric, peripancreatic and periportal lymph nodes
2212	43	White F	Ossified, calcified primary focus, 3 mm., right lower, with extensive calcification of all regional bronchopulmonary, lower and upper tracheobronchial and paratracheal lymph nodes on the right side	Chronic fibrous cheesy changes in apex and subapical area of right upper with minimal chalky-calcified lesions. Older chalky-fibrous pleuritis around right lung especially above the diaphragm. More recent peribronchial tuberculosis in left lower with recent hemorrhagic tuberculous pleuritis around left lung. Recent caseation in lymph nodes regional to right upper. Casated conglomerate tubercles in all bronchomediastinal and supradiaphragmatic lymph nodes, extending into right angulus nodes	Tuberculous pericarditis and peritonitis. Few hematogenous tubercles in liver, kidneys and left lung. Caseation of mesenteric, periaortic and peripancreatic lymph nodes
2279	28	White M	Single calcified-ossified focus, 1 mm., in middle third right upper. No old lymph node changes regional to focus	Several pea-sized fibrous tubercles, especially in subapical portion of right upper and in different parts of right lower. Lymphogenous progression to lymph nodes draining right lower; no tuberculous changes in lymph nodes regional to right apex; no tuberculosis in lymph nodes regional to left lung	Scattered miliary tubercles in both lungs. Tuberculoma of pons. Miliary tubercles in prostate, kidneys, liver and spleen. Few small ulcers in lower ileum, with progression to one mesenteric lymph node
2425	19	White M	Firmly calcified, with two pinhead-sized foci in left lung, upper third left lower and middle part left upper. Calcification of one regional intrapulmonary and one interlobar bronchopulmonary lymph node	Extensive casated tuberculosis left lower, with wedge-shaped, cherry-sized casated lesion. Fairly diffuse caseation of left bronchopulmonary and left lower tracheobronchial lymph nodes. Fairly marked intrabronchial spread to lower part left lower and to right lung, especially lower. Apices free. No tubercles in lymph nodes regional to right lung	Extensive hematogenous seeding in spleen and liver. Tubercles in spleen of considerable size, with cavitations in centre. Casated conglomerate tubercles in peripancreatic lymph nodes. Rare epithelioid tubercles in bone marrow. Few tuberculous infiltrates in kidneys

2503	41	White M	Single ossified-stony focus, 1 mm., subpleural, lateral field right upper. Minimal complex changes in regional bronchopulmonary lymph nodes	Fibrous chalky tuberculosis in most of subapical part left upper, with several cavities. Few recent cavities also in left lower and right upper. Complete adhesion of left upper. Fibrous chalky tuberculosis of bronchopulmonary lymph nodes regional to left upper	Fibrocaceous tuberculosis of kidneys, prostate, bladder and left adrenal. Death from recent tuberculous meningitis. No tubercles in brain substance. Few fibrous tubercles in liver and spleen
3304	49	White M	Calcified complex with minute primary lesion in right subapical area. Firm calcification of close-by intrapulmonary lymph node and a few splinters in one regional upper tracheobronchial node	Cavity, 2 x 1 cm., in lower third right upper, and 4 x 5 cm. in midportion of left lower. Recent intrabronchial spread through left lower. Recent lymphogenous progression to both lower and upper tracheobronchial lymph nodes, especially on the left side	Extensive ulcerative intestinal tuberculosis; excision of mesenteric lymph nodes, progressing into thoracic duct. Dense milary tuberculosis of lungs, spleen, kidneys, liver and pancreas
4704	20	White M	Two stony ossified, pea-sized foci, upper part left lower. Firm stony calcification of regional bronchopulmonary and lower and upper tracheobronchial nodes, crossing from left hilum to right upper tracheobronchial, paratracheal and right angulus nodes. Old single focal extension to base of right lower	Three firmly caseated foci between 1 and 1.5 cm. diameter, with central chalky deposits, right subapical area, posteriorly, near mediastinal pleura, with edematous band adhesions to mediastinal pleura. Active tuberculous granulation tissue around the large caseated tubercles. No recent lymph node tuberculosis regional to area of reinfection	Typical tuberculous meningitis and a few tubercles in liver and kidneys. No tubercles in brain substance
5091	60	White M	Two or three firmly calcified and ossified complexes. Pea-sized stony ossified foci in each lower, and hilar area of each upper, complicated by considerable anthraco-silicosis. Firm calcification of all bronchopulmonary, posterior mediastinal and lower and upper tracheobronchial lymph nodes, more marked on the right	Chronic fibrocaceous tuberculosis in left apex. Unusually marked caseated bronchitis and peribronchial tubercles around and below the left apex. Recent tubercles in anterior mediastinal lymph nodes on left side. Peribronchial tubercles in right lower and right upper	Very dense milary tuberculosis of both lungs, spleen, liver and kidneys. Zenger degeneration of both recti abdominis muscles
5453	72	White M	Stony ossified, base left lower, with lentil-sized, primary focus. Firm calcification of regional bronchopulmonary lymph nodes	Older fibrocaceous lesion with recent cavitations, apex of right upper. Few hyaline-fibrous-chalky tubercles in lymph nodes regional to right upper, including right angulus lymph nodes. Massive intrabronchial spread within right upper, right lower and base left lower. Diffuse tuberculous hyperplasia with central necrosis of anterior mediastinal and left upper tracheobronchial lymph nodes. A few epithelioid cell tubercles in both lower tracheobronchial lymph nodes	Extensive hematogenous tuberculosis in both kidneys with small "tuberculous abscesses." Milary tuberculosis of both lungs. Tuberculous meningitis

TABLE 1—Continued

CASE NUMBER	AGE	RACE AND SEX	STATE AND SITE OF PRIMARY COMPLEX	LOCATION, ANATOMICAL TYPE AND EXTENT OF THE REINFECTION LESIONS	HEMATOGENOUS LESIONS AND VARIOUS ADDITIONAL OR SPECIAL FINDINGS
4740	64	White F	Two firmly calcified complexes; one pinhead-sized focus in right lower, one in left upper. Firm stony changes in all bronchopulmonary, lower and upper tracheobronchial and paratracheal groups	Localized chalky-fibrous tuberculosis, subapical, left upper. Fibrocascous and older hyalinized tubercles, but also few recent caseated conglomerate tubercles in left lower paratracheal lymph nodes	Massive milary tuberculosis in lungs, liver, spleen, kidneys and adrenals
4838	77	White F	Calcified-ossified, primary focus obscured. Firm stony changes in left upper bronchopulmonary group	Fairly symmetrical ossified-calcified tubercles, apical and subapical area, both upper lobes, combined with fibrocascous and caseous tuberculosis throughout right upper, right middle and upper half of left upper, with considerable tuberculous bronchitis. Firm calcification with some ossification of a few intrapulmonary lymph nodules. Hyaline oblong and nodular tubercles in anterior mediastinal and in a few bronchopulmonary lymph nodes, especially on left side	Massive caseation of adrenals (death from Addison's disease). Caseation of periaortic and retromediastinal nodes. Few caseated tubercles in liver, spleen and peripancreatic lymph nodes
4051	26	White M	Firm stony formation in several mesenteric lymph nodes	Progressive fibrocascous tuberculosis in both upper lobes. Recent cavities filled with bloody, caseated material in right subapical area and in middle third left upper. Scattered lentil-sized chalky tubercles in right upper and upper part right lower. Recent intrabronchial spread through both upper and upper parts of both lower. Complete adhesions about both lungs. Tuberculous hyperplasia of anterior bronchomediastinal and upper tracheobronchial lymph nodes, especially on right side	Many milary tubercles in all lobes of both lungs. Tuberculous meningitis; caseation of tela choroidea of third ventricle. Two pea-sized tubercles in cerebellum and medulla. Scattered bile duct tubercles in liver

chronic hematogenous tuberculosis of various organ systems *in the absence of exogenous reinfection lesions* in the lungs or in the intestinal tract. This chronic hematogenous tuberculosis, in particular, appears dependent only on the primary tuberculous complex, including its original or indirect sequelae. The presentation of the anatomical material included in the present paper seems to indicate that chronic (so-called protracted) hematogenous tuberculosis is not necessarily or exclusively the result of primary tuberculous infection. In fact, anatomical findings and history in some cases of our series point to a chronic disease in the course of which considerable extension of the tuberculous process by the bloodstream did occur. But this extension, we feel, was secondary to and not causative of the chronic pulmonary lesions.

We have selected 12 cases, listed in table 1, to demonstrate various forms of hematogenous tuberculosis secondary to exogenous pulmonary super- or reinfection lesions in adults. In each of these cases included in this series the anatomical findings in their relation to course and symptoms of the disease are of sufficient interest that they would justify a more detailed description. The variety of these findings in relation to the variety of clinical symptoms, duration and progress of the disease, with its true nature frequently not recognized clinically, demonstrates again the highly individual problems inherent in the disease tuberculosis, as it presents itself in the evolution of the clinical picture and in the morphological changes seen postmortem in many an individual case.

There is so far meagre information, morphologically substantiated, on the incidence of chronic hematogenous pulmonary tuberculosis caused by delayed lymphohematogenous metastatic spread from the primary complex. We have quoted already in a previous paper (no. XV) Schuermann's statement that fatal cases of protracted hematogenous tuberculosis amounted to about one-third of those with typical phthisis. Schuermann apparently did not imply that these were caused by protracted hematogenous spread from the primary complex. In the report on his figures on the closed complex, Schuermann states further that in 20 to 30 per cent, in addition to a stony complex, postprimary pulmonary lesions were found incidentally, which originated either from superinfection or from hematogenous seeding. In all cases of protracted hematogenous tuberculosis the pulmonary foci due to aspiration from the hematogenous tubercles were small, while phthisis always resulted in marked aspiration. Discussing, more specifically, isolated foci in prolonged hematogenous generalization, Schuermann found that they are more apt to caseate than bronchogenic foci in pulmonary tuberculosis. He was obviously not under the impression that the pulmonary foci caused by hematogenous lesions, although leading to isolated tubercles within the walls and lumina of bronchi, would initiate progressive intrabronchial (phthisic) spread. Chronic phthisis, on the other hand, is apt to lead to chronic miliary tuberculosis, but not to the acute overwhelming type.

If, in clinical studies carried out over three years, 20 to 30 per cent of the cases of pulmonary tuberculosis could be "reasonably ascribed to hematogenous dissemination" by Miller (1), careful morphological analysis should show how far the observations of Miller can be coördinated with the final morphological pic-



tures seen postmortem in these cases. For Miller's belief that hematogenous disseminations restricted exclusively to the lungs are "very likely to occur," we could not find any proof on the basis of our own postmortem studies. Nor can we agree with Murano (2) that chronic miliary tuberculosis in infancy, in connection with the lymphoglandular lesions, is limited to the lesser circulation. Rare instances in which, together with an obsolete primary intestinal complex, a few (four to six altogether) single calcified minute miliary tubercles were found in both lungs (paper XIII) can be excluded from this discussion; they were of no clinical significance.

Miller, on the other hand, in apparent accord with Schuermann, has called attention to the clinical experience that lesions of chronic hematogenous pulmonary tuberculosis show "a remarkably sluggish productive character . . . persisting over periods of years without much progression." We shall report in one of the following papers two anatomical postmortem observations of such cases of chronic hematogenous, large nodular disseminations to the lungs, spleen and liver, in connection with several primary complexes. These findings, however, were only incidentally discovered in both cases. There was no history of any tuberculous disease at any time. Miller has also stated that hematogenous pulmonary foci have been observed, capable of absorption in all other parts until only apical or upper lobe foci remained and progressed to calcification. According to Duken (3), too, the healing tendency of miliary tubercles in the apices was less than in other parts of the lungs.

Against these clinical observations, however, stands Loeschke's (4) statement that it is anatomically impossible to prove the hematogenous nature of disseminated lesions, shown in the X-ray picture. Nor can the figures of Cohen (5) on hematogenous tuberculosis be accepted as anatomically proved. Of 246 cases, in 61 per cent the diagnosis of "hematogenous tuberculosis" was made. In all of them the duration of the illness was one year or less. Postmortem findings were given of 20 cases. Unfortunately, the careful clinical observations of Cohen are not supplemented by morphological analysis of the same order. The source for the hematogenous dissemination is by no means clarified. As with other anatomical reports added to valuable clinical observations, to mention especially those of Rubin (6), the morphological analysis is not sufficiently systematic and detailed to prove the hematogenous character in those cases in which postmortem examination was performed. In a brief anatomical report given by Rubin, presenting a case of extensive ulcerated laryngeal tuberculosis as hematogenous, there is nothing contained to prove the blood-borne nature of laryngeal tuberculosis in this case. In fact, the presence of cavities in the lung makes the intracanalicular pathway appear as the most likely one.

In a paper on the evolution of hematogenous pulmonary tuberculosis into bronchogenic tuberculosis (7), Cohen claims that focal miliary pulmonary tuberculosis produced miliary lesions usually confined to the upper portions of the lungs. If these hematogenous parenchymatous lesions, varying from miliary to conglomerate nodular size, progress, they might coalesce, caseate and excavate, with subsequent intracanalicular spread. We are faced here again with the same

assertion alluded to in the discussion of the "Simon's foci" in two preceding papers (nos. XIV and XV). For the pathologist familiar with embolic phenomena, it is difficult to comprehend why miliary hematogenous lesions should be "usually" restricted to the upper fields. In cases of anatomically proved, acute overwhelming miliary tuberculosis or with chronic hematogenous nodular disseminated lesions, all parts of both lungs are uniformly involved, provided there is no difference in the air content of the individual lobes, especially no atelectasis. In these cases of typical hematogenous miliary or chronic nodular seeding to the lungs, no restriction to the upper fields has been seen so far postmortem.

Our anatomical material is arranged in table 1. (For lack of sufficiently complete histological control we had to exclude 2 cases which, on the gross-anatomical basis, most probably belong in the same group.) The following 5 cases will be presented in some detail (see table 1: nos. 2425, 4764, 5091, 5453 and 4888).

#### CASE REPORTS

*Case 1:* (B. G. H. 2425) Nineteen year old white male. Cause of death: chronic miliary tuberculosis. (Plate 1)

There are two firmly calcified, pinhead-sized foci, one in the upper third of the left lower lobe, the other in the midportion of the left upper lobe. The histological picture of these foci shows early stone formation, encased by hyaline bands. In both of them, the concentric, ring-like layering (Liesegang) is clearly visible in the photographs A and D. The tubercle in the upper lobe (A) appears in a distinctly firmer calcified state than the tubercle in the lower lobe (D). There is no ossification in either. One bronchopulmonary node at the hilum of the left lower lobe and one intrapulmonary lymph nodule in the left upper lobe (B) close to the parenchymatous focus show compact calcification of the same character as found in the pulmonary foci. There are no other older chalky or calcified lesions in any lymph node draining both lungs. These four lesions represent the result of the primary infection, for the most part in firmly calcified state, possibly consisting of two restricted complexes, one in the left upper, the other in the left lower.

In addition, a cherry-sized, wedge-shaped, firmly caseated bronchopneumonic lesion is found in the lateral area of the middle third of the left lower lobe, extending to the pleura, which contains about 500 cc. of hemorrhagic and slightly fibrinous exudate. There are a few pea-sized, firmly caseated tubercles surrounding this focus. Underneath the fibrinous exudate covering the visceral pleura, many pinhead-sized tubercles are seen, apparently all situated within the pleura. One left interlobar and one left bronchopulmonary and lower tracheobronchial lymph node show fairly diffuse caseation, although they are not enlarged. The visceral pleura of the left upper lobe shows also a few scattered miliary tubercles underneath fibrinous exudate. But only in its lower part there are hemorrhagic foci in distinctly peribronchial distribution, histologically of tuberculous nature. Intrabronchial spread within the left lower lobe from the large focus in its middle third was considerable, especially in the basal portions of this lobe. In the right lung there are recent tuberculous lesions of distinctly bronchitic and peribronchial, acinous type, with considerable hemorrhages along the tuberculous lesions. These changes are present in all lobes, except for the apical portion of the upper. There is also recent fibrinous pleuritis, but no tuberculosis in the lymph nodes draining the right lung.

There is very marked hematogenous tuberculosis in the spleen, liver and kidneys. The tubercles in the spleen, in particular, are from pinhead- to hazelnut-size with central cavitation in the larger ones. The spleen is increased, weighing 625 g., and shows a few

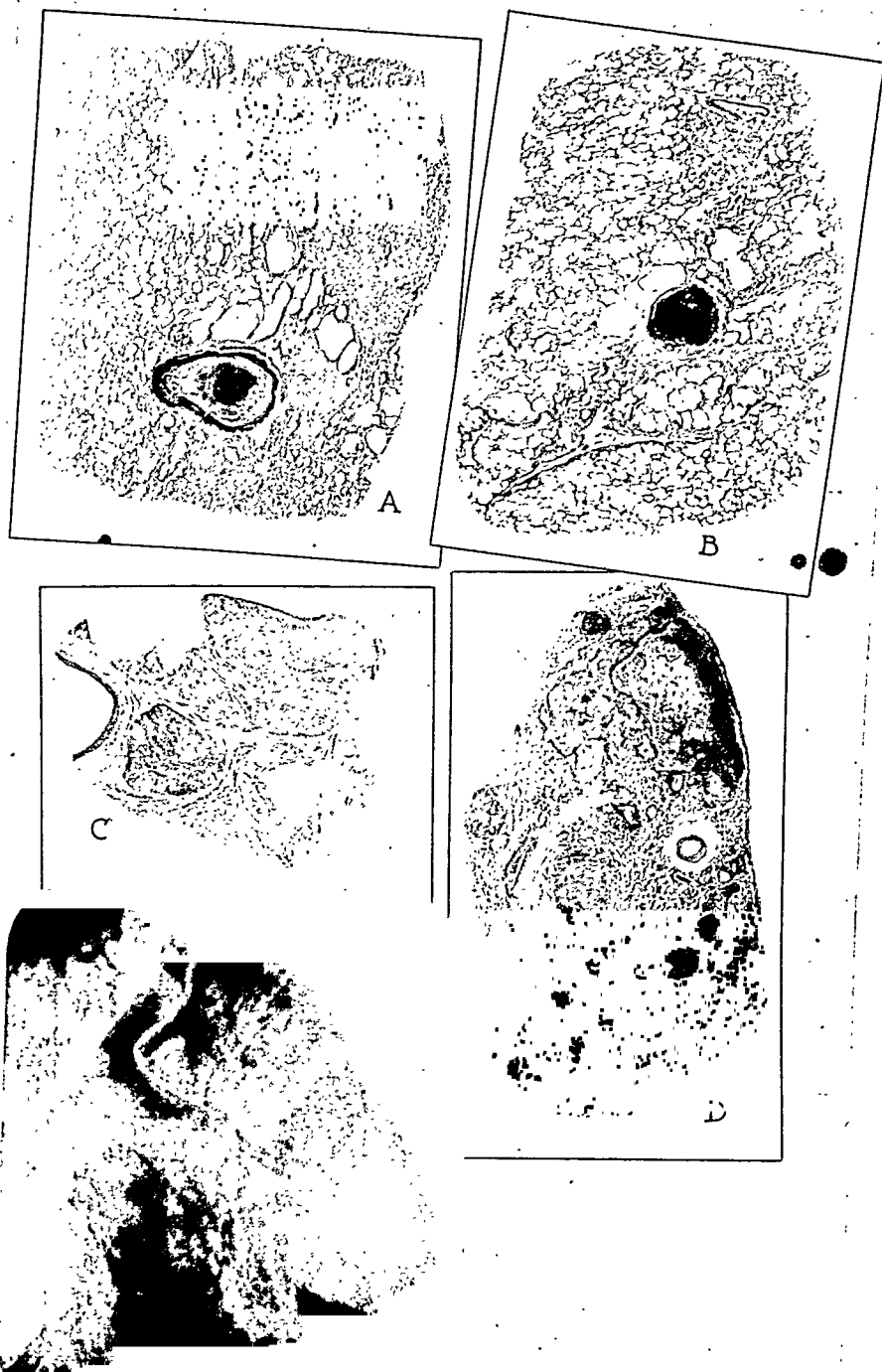


PLATE 1

tuberculous infarcts. The gross appearance of the spleen resembles somewhat the "suet-like" pattern in Hodgkin's disease. Innumerable tubercles are seen also in the liver, some of them nearly the size of a small pea. The peripancreatic lymph nodes contain caseated conglomerate tubercles. There is no tuberculosis in the gastro-intestinal tract. Microscopically, a few epithelioid cell tubercles are also found in the bone marrow.

This case had been included in one of our preceding papers on recent primary tuberculosis in adults (8). A brief report was given (page 90) and the findings interpreted as a primary tuberculosis with protracted hematogenous spread. It was stated that "the picture in the lungs is too complicated to determine whether or not the extensive intrabronchial spread was preceded by hematogenous spread to the lungs; most probably the processes coincided." The large caseated focus was considered as belonging to the primary infection. Reëxamination of the entire specimen, which had been saved in formaldehyde in order to examine histologically the relation between the chalky-calcified centre and the surrounding caseated lesions, seems to suggest that we are dealing with two episodes of exogenous infection. Serial sections were made through the large lesion and the close-by calcified-chalky focus. In all sections this lesion appeared completely walled off from the surrounding tissue by a rather thick hyaline capsule. Also, the restricted complex changes, in a firmly calcified state, not extending beyond one bronchopulmonary and one intrapulmonary lymph nodule, do not speak in favor of further lymphogenous and hematogenous progression. There is no anatomical sign of "reactivation" of the primary tubercle proper nor of its capsule. We believe, then, that the large wedge-shaped lesion in the left lower lobe, in spite of its close proximity to the chalky-calcified primary tubercle, is actually the result of a superinfection or reinfection. In favor of this conception are the complex-changes to this postprimary caseated tuberculosis which are likewise recent and more diffuse and regional to the left lower lobe only. The photograph (D) shows very clearly one of the old primary tubercles encased by a broad hyaline band and the spreading bronchial and peribronchial caseated tuberculosis with early disintegration in the centre of the large tubercles. The extensive caseation with a few caseated conglomerate tubercles is also clearly seen in the photograph (C), presenting two bronchopulmonary lymph nodes from the hilum of the left lower lobe.

It is remarkable that neither grossly nor histologically could we demonstrate any miliary tubercles in the parenchyma of both lungs, although the pleural surfaces, especially on the left side, showed a considerable number of recent tubercles. The histological picture in the recent caseated lesions in the lungs was somewhat unusual, inasmuch as necrobiosis was very pronounced along with diffuse caseation, while in spite of the typical peribronchial spread it was rather difficult to recognize this lesion as tuberculous by its histological structure. The picture in the lymph nodes, however, as can be seen even from the low power photograph, was typical of tuberculosis, with many Langhans' giant cells, typical epithelioid cells, caseated necrosis and but moderate fibrosis.

One of the most interesting features in this case was considerable proliferation of reticulum cells in all the lymph nodes examined which were grossly not tuber-

culous, especially in those taken from the bronchomediastinal groups. It resembled slightly the uniform hyperplasia of reticulum cells seen in so-called reticulosis. In this connection, the history of the patient is of unusual interest. He was admitted on June 28, 1933. His illness had, at that time, already lasted two months. He had almost daily chills, with fever and progressive weakness. Several abscesses in the integument developed, from which staphylococci were recovered in pure cultures. His spleen became palpable. The X-ray film showed only large hilar shadows. The temperature curve suggested a septicemic process. All blood cultures remained persistently negative. A diagnosis of undulant fever, tularemia and various other infectious diseases, except hematogenous tuberculosis, was entertained, but all respective bacteriological and especially immunological tests remained persistently negative. The patient had, however, productive cough during his hospital stay. In the last week before death he complained of stiffness of the neck. It was thought that this might be due to an intracranial lesion, possibly an abscess. The spinal fluid was not examined, as the patient was rapidly failing. He died on the 30th of October. Unfortunately, there was no permission obtained for examination of the brain. Whether or not there were hematogenous tubercles in brain or leptomeninges could not be decided. Hematologically, this case first had shown a high percentage of immature white cells (25 per cent myeloblasts and 22 per cent myelocytes), suggestive of acute myeloblastic leukemia. As in successive examinations this percentage decreased considerably, the hematological diagnosis leaned strongly in favor of a stimulation myelosis as a result of infection (Dr. Stuart Vaughan).

This case, we feel, represents a progressive hematogenous tuberculosis in connection with a recent superinfection or reinfection of the left lower lobe, with recent complex changes in a few lymph nodes draining this lobe. The apparent absence of miliary parenchymatous tubercles along with considerable hemorrhages around the typically intrabronchially spreading acinous lesions point, in our opinion, to a progressive reinfection or superinfection as the source of the very marked hematogenous dissemination to spleen, liver, kidneys, and, to some extent, to the bone marrow. Note also the absence of tuberculous lesions in the apices of both upper lobes and in the left subapical field. The tuberculous lesions in the right subapical field had the typical gross and histological appearance of recent peribronchial tuberculosis, as seen in recent intrabronchial spread.

*Case 2:* (B. G. H. 4764) Twenty-nine year old white male. Cause of death: tuberculous meningitis. (Plate 2)

There is a primary complex with two firmly stony foci, in part in ossified state, situated in the uppermost portion of the left lower lobe, with extensive calcification of the lymph nodes around the hilum of the left lung, crossing over to the entire lymph node chain on the right side of the trachea, including one lymph node in the right venous angle. All these lymph nodes, grossly and microscopically, are in a firm stony condition, with the large, conglomerated, firmly calcified tubercles entirely encased by hyaline capsules.

In typical subapical position in the right upper lobe, 3 to 4 cm. below the apex, there are three firmly caseated and slightly chalky, encapsulated foci, varying in diameter between 1 and 1.5 cm. They are in the most posterior portion of the right upper lobe. The vis-

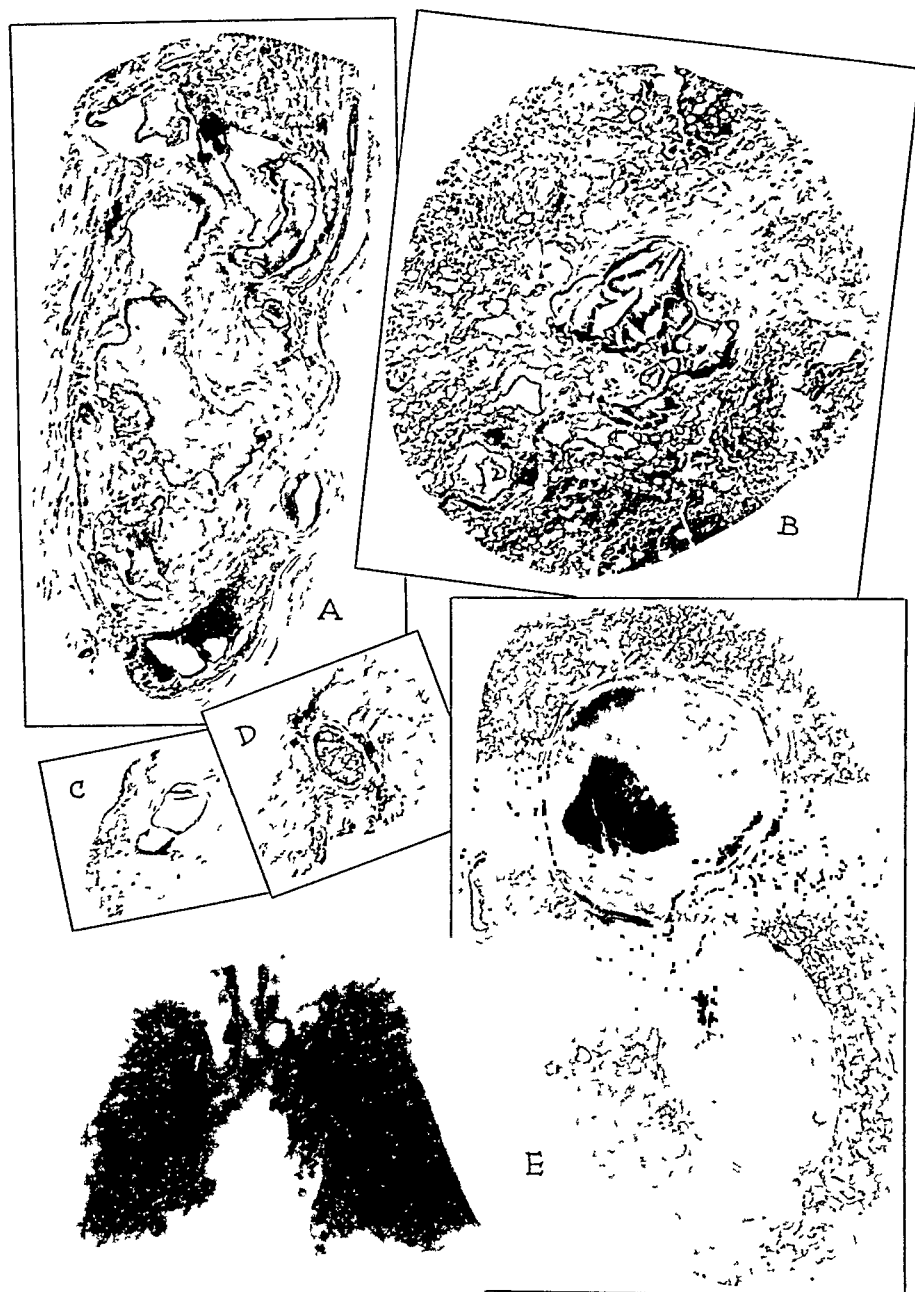


PLATE 2

ceral pleura above these subpleural lesions is fixed to the mediastinum by distinctly edematous band adhesions. There are no recent caseated or chalky lesions in the lymph nodes draining the right lung. The other anatomical findings include a diffuse tuberculous meningitis of recent nature with a great deal of exudate in the basal cisternae and a few small caseated tubercles in the tela of the third ventricle and in the choroid plexus of both lateral ventricles, a few minute subcapsular soft tubercles in the liver and a few irregular tuberculous infiltrations in the kidneys. There are no tubercles in the substance of the brain, nor are there any miliary tubercles in the lungs. Already, before histological examination, it was felt that this observation presented a classical example of a subapical reinfection in the presence of a completely petrified primary complex with two primary foci in the opposite lung. It was clear, grossly, that the hematogenous tuberculosis of the leptomeninges could have been caused only by the reinfection lesion in the right upper lobe.

The histological examination was as complete as possible, including the primary stony lesions in the left lower lobe, the completely calcified lymph nodes in the left pulmonary ligament, the left bronchopulmonary nodes, the left lower tracheobronchial lymph nodes, a few left peribronchial and upper tracheobronchial nodes, the right paratracheal lymph nodes, the lymph nodes along the innominate artery and the lymph nodes in the right venous angle. In addition, all other lymph nodes draining the right and left lung were examined, in order to rule out the presence of lymphogenous reactivation or recent tuberculous lesions in lymph nodes regional to the right upper lobe. All lymph nodes in both venous angles were completely examined and all bronchopulmonary lymph nodes in the hilar area of the right upper lobe. Also, the entire subapical field of the right upper lobe with the reinfection lesions and a few minute calcified lesions in the base of the right lower lobe.

*Histological report:* Plate 2 shows the photographs of the primary focus (B) and a second calcified parenchymatous tubercle (C) in the same area of the left lower lobe. Both are firm, ossified stony lesions surrounded by markedly hyalinized fibrous tissue, the larger focus already in process of fragmentation along a segment of its periphery. Part of the surrounding lung tissue, on the photograph to the right of the focus, shows localized collapse-induration. In the larger focus there is a fair amount of bone marrow encroaching upon the firmly stony core. One of the small calcified nodules found at the base of the right lower lobe is also a completely calcified stony tubercle surrounded by a bony shell, with the alveolar pneumonic pattern still recognizable in the decalcified section (D). This, we believe, is a typical focal extension from the primary focus in the opposite lung. A section through the large right paratracheal lymph node is shown on photograph A. These large, completely petrified tubercles, replacing almost the entire original structure of the lymph node, show extensive bone formation and calcification. Some of the calcified matter, as clearly seen in the photograph, is in process of progressive resorption by lymphoid marrow and fibrous tissue. All stony lymph nodes forming the large primary complex show exactly the same picture as presented on photograph A. All these tubercles are in firm, stony state, and especially the smaller conglomerate tubercles show evidence of progressive resorption of the stony matter. There are, in addition, a few firmly hyalinized, fibrous tubercles, especially in the lymph nodes of the left pulmonary ligament and the left lower tracheobronchial group. Two lymph nodes in the right venous angle contain large stones encased within a broad, firm hyalinized capsule. All the other lymph nodes mentioned above, including several soft lymph nodes within the calcified chain regional to the left lung and all lymph nodes draining the right lung in addition to all grossly not calcified lymph nodes belonging to the group in each venous angle, are histologically entirely negative. No recent tuberculous lesions are present in any of these lymph nodes.

Photograph E shows one of the sections through the reinfection lesions in the right subapical area. Note the firm, caseated lesion with some chalky material near the centre and the distinct progression of the tuberculous process around the capsule of the large tubercle in the lower field of this picture. There is much more microscopic progression of the tuberculous process than was anticipated grossly, with distinct conglomerate tubercles with central caseation and with early disintegration in the caseated centre of the larger nodules. There are also a few interstitial miliary tubercles very close to this area, apparently within lymph vessels close to the periphery. The sections taken through the edematous band adhesions above the large caseated subapical lesions do not show specific tuberculous changes. There is only unusually marked edema with considerable new formation of small arterial and venous capillaries. Some of the large, completely caseated tubercles are encroaching upon this edematous pleural tissue. The remaining small calcified lesions in the lower lateral field of the right lower lobe are typical "osteomata" within alveoli.

A pathologist is rarely in a position to analyze a case of reinfection as completely as it has been done in this case. The reinfection lesions are comparatively restricted, and the entire area could be examined in selected serial sections. The two primary lesions together with the additional tubercle in the opposite lower lobe are in an entirely obsolete, petrified-ossified state. The unusually extensive complex, involving the entire homolateral lymph node groups and crossing to the contralateral lymph nodes along the trachea, innominate artery and in the venous angle, show entirely coördinated, petrified lesions of obsolete type. An endogenous reactivation in one of these lymph nodes or in several noncalcified lymph nodes between or within these groups can be ruled out, including the mediastinal groups, as there were no recent tuberculous changes in any lymph node regional to either lung. The gross and histological appearance of the reinfection lesions, quite typically localized in the right subapical field, shows a relatively recent state of this tuberculous process with very distinct active progression around all three reinfection foci. The largest of these is clearly visible on the X-ray photograph, presenting an opaque shadow with some of the chalky material faintly marked. There is no question that this relatively recent reinfection was the source of hematogenous spread to the leptomeninges. Since the lymph nodes regional to the right upper lobe, all of which were examined histologically, did not show any sign of lymphogenous progression from the reinfection lesions, the invasion of the blood-stream was either directly within the lung tissue or was conveyed through venous collaterals within the soft adhesion membranes connecting the right upper lobe with the paravertebral tissue.

At the present time we merely want to call attention to the development of diffuse tuberculous meningitis in the absence of massive miliary seeding and especially in the absence of active tuberculous lesions in the lymph nodes draining the area of pulmonary reinfection, and in the absence of hemorrhages in or around the recent reinfection lesions. It will be necessary to observe more cases with a similar, so peculiarly selective spread of a tuberculous reinfection to the leptomeninges before more may be said as to the possible significance of venous anastomoses between the mediastinal pleura and intraspinal venous plexus, forming a direct hematogenous pathway.

This case, on the other hand, demonstrates clearly that tuberculous meningitis can be caused by a relatively small reinfection lesion restricted to one subapical area. The structural age of the pulmonary lesions in the right subapical field is so different from all parenchymatous pulmonary and lymph node tubercles com-



posing this unusually extensive and petrified primary complex that any pathogenetic relation between these two processes can be discarded. This extensive histological analysis has proved that the lesions in the right subapical field can be explained in no other way but as the result of an exogenous reinfection.

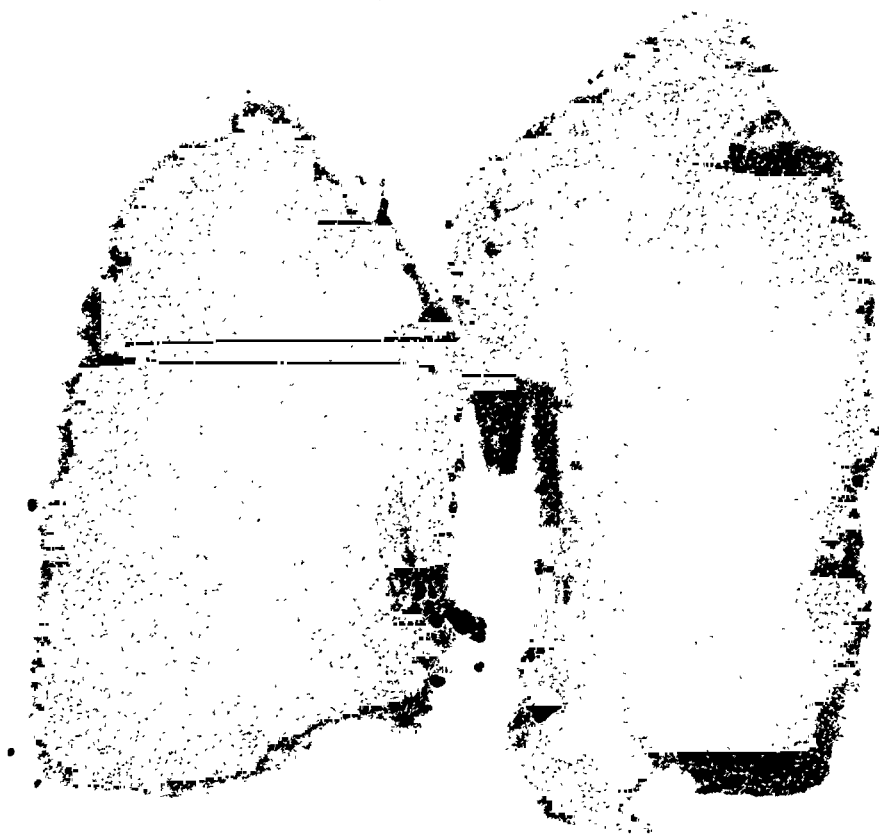
There is only a brief history available in this case. The patient was admitted on May 14, 1941. He had suffered from "flu" in February of that year. His first symptoms, at that time, were constant backache for the last three weeks, nausea and vomiting. In the last three days he showed considerable stiffness of the neck. No X-ray film was taken. On physical examination the chest was found clear and resonant. The picture of meningitis was already well established on the day of admission. Tubercle bacilli were found in the spinal fluid. The patient died on the 18th of May, on the fourth day following his admission.

*Case 3:* (B. G. H. 5091) Sixty year old white male. Cause of death: miliary tuberculosis. (Plates 3, 4 and 5)

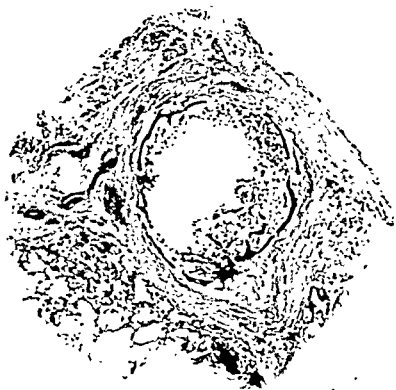
Only a very brief summary of the gross and histological findings will be given in this case. There are two or possibly three firmly calcified, ossified complexes of first infection, with one pea-sized, ossified, stony lesion in each lower lobe. There is unusually marked calcification and ossification of several bronchopulmonary and lower and upper tracheo-bronchial lymph nodes, especially on the right side (C), and of the lymph nodes in each pulmonary ligament. These changes are markedly complicated by considerable anthracosilicosis. Most of the compact whitish nodular shadows, especially in the peripheral pulmonary fields but also near the mediastinal borders of the lower lobes, seen in the roentgenogram (A), are anthracosilicotic nodules. In fact, only in the right lower lobe one of the firmly calcified lesions can be clearly diagnosed as an old stony tuberculous ossified focus, containing a great deal of lymphoid and fat marrow (plate 3, B). There is, however, considerable bone formation also in the anthracosilicotic subpleural lymph nodules. In the right upper lobe there is one focus almost completely replaced by bone marrow, surrounded by a thin bony shell. The other calcified foci in this lobe are apparently anthracosilicotic intrapulmonary lymph nodules.

In the left apex and in the central and lateral part of the left subapical field there is the typical picture of chronic fibrocased tuberculous with localized intrabronchial and peribronchial spread. The left lung is entirely adherent and shows callous thickening of the pleura in some areas around the left upper and left lower lobe. The histological picture of sections taken from the left upper lobe (plate 4, D and E) shows a typical chronic caseated process with extensive tuberculous bronchitis and peribronchially spreading acinous tuberculosis. A few lymph nodes in the anterior mediastinal group attached to the left upper lobe contain recent caseated tubercles which were already recognized with the naked eye. There is, in addition, unusually massive and dense miliary tuberculosis involving uniformly both lungs, with the miliary tubercles having an average diameter of 1 mm. (F). The spleen is distinctly enlarged, weighing 450 g., and studded with innumerable minute miliary tubercles hardly recognizable with the naked eye. Dense miliary tuberculosis is present also in the liver, and there are many conglomerate tubercles in the cortex of both kidneys, grossly appearing as tuberculous infiltrations.

Apparently in connection with this overwhelming acute miliary tuberculosis there was a fairly symmetrical hemorrhagic myositis of each rectus muscle in the abdominal wall, with a fair amount of fluid blood accumulated between the muscle and its posterior sheath, and many obvious ruptures of muscle fibres. A large number of sections taken from both



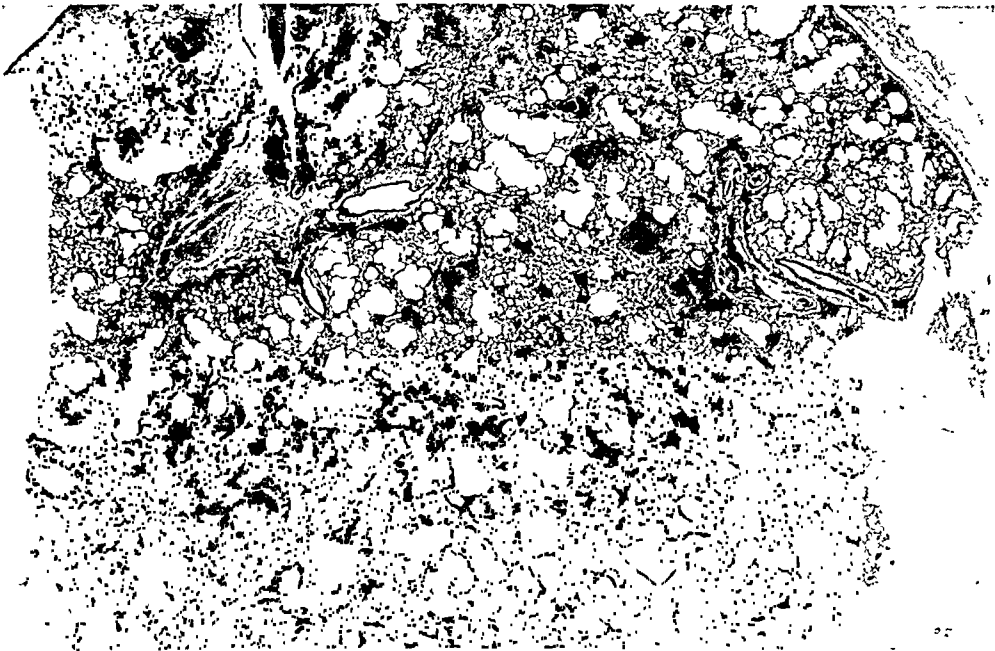
A



B



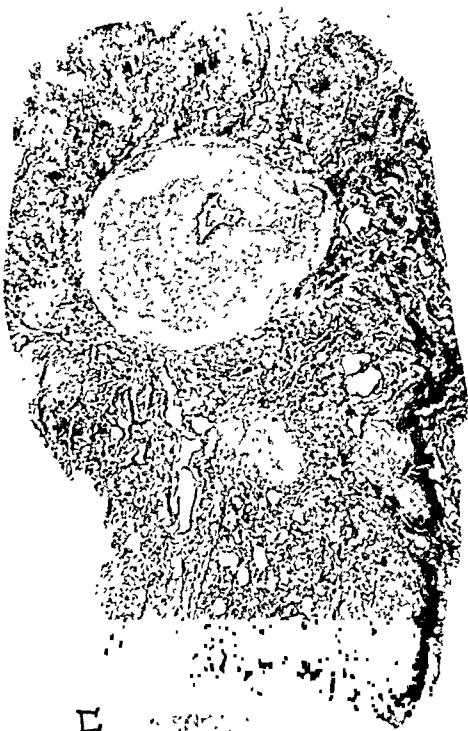
C



F



D



E

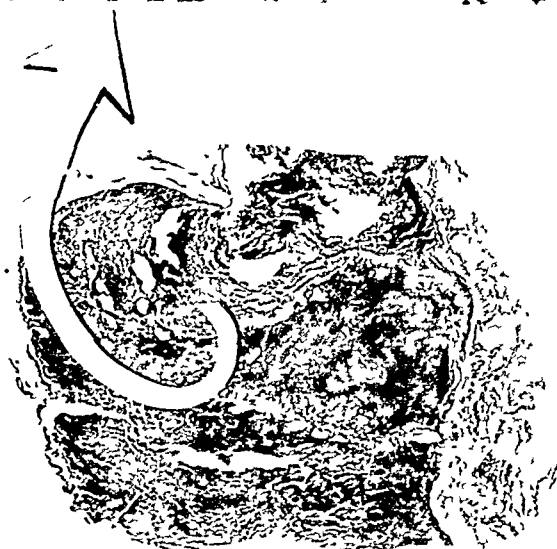
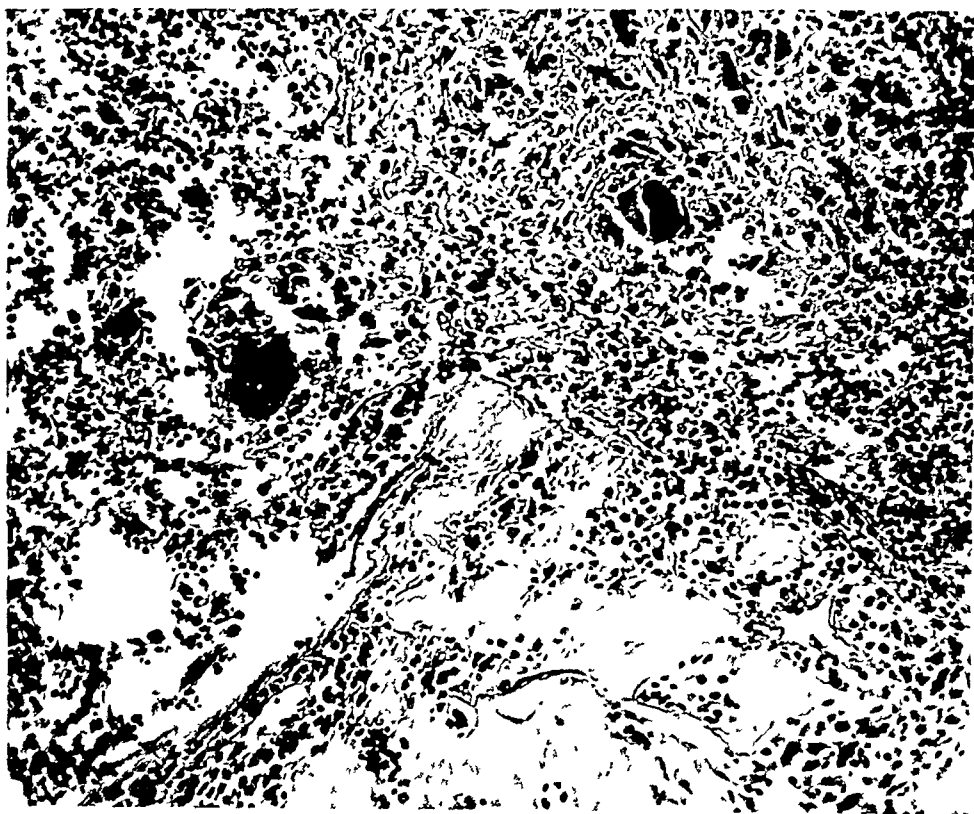


PLATE 5

recti muscles show histologically extensive anemic necrosis with diffuse hemorrhages surrounding the necrotic muscles. There is a variety of degenerative changes, including hyaline degeneration, vacuolar liquefaction and fragmentation, along with unusually marked swelling of individual fibres. Interstitial inflammatory infiltrations with considerable proliferation of perimysial cells and myogenic giant cells conclude this impressive picture of acute nonspecific myositis with Zenker degeneration.

In view of the anatomical findings, the hospital record contains some interesting notes. This patient was admitted on June 23, 1942, and died on the 4th of July. Four years previously he had pleural pneumonia. Since February there was a steadily increasing anorexia, and of late, preceding his admission, there was increased cough and a chilly feeling. The most impressive symptom, however, was severe abdominal pain radiating to the back and epigastric pain described as "feeling like nails," obviously caused by the acute degeneration of the recti muscles. The clinical impression was typhoid fever—with a question mark. The roentgenological examination showed miliary mottling in the presence of left apical infiltration, diagnosed as miliary tuberculosis.

In spite of unusually marked changes of anthracosilicosis in the pulmonary lymph nodules as well as in tracheobronchial and mediastinal lymph nodes, in sections taken from a few anterior mediastinal nodes regional to the left upper lobe the recent tubercles appeared as independent lesions although closely encroaching upon the large old calcified stones (plate 5).

*Epicrisis:* There are at least two, or possibly three, firmly calcified and ossified complexes of first infection with two parenchymatous primary foci in the right lower and right upper lobe, and with the third focus, complicated by silicosis and not clearly identified, in the left lower lobe. These foci as well as the lymph nodes are in a firmly calcified-ossified state. There are no changes of endogenous-lymphogenous reactivation. The pulmonary reinfection lesion is of typical location, restricted to the apex and a considerable area in the left subapical field, in a chronic fibrocaseated state, with very marked localized active intra- and peribronchial spread within the upper half of the left upper lobe. Recent lymphogenous changes, apparently secondary to the reinfection lesions, were found only in a few anterior mediastinal lymph nodes close to the left upper lobe, the entire left lung being adherent to the parietal pleura. There was no trace of any hematogenous tuberculosis in connection with the old obsolete primary complex. The gradually progressive reinfection lesion of the left upper lobe is the only source for an overwhelming acute miliary tuberculosis, affecting uniformly both lungs, liver, spleen and kidneys. Whether or not this acute overwhelming hematogenous tuberculosis originated directly within the active lesions of the left subapical area, or whether it was brought about by recent lymphogenous spread to several anterior mediastinal lymph nodes regional to the left upper lobe cannot be decided. Unusually marked anthracosilicosis in firm calcified and ossified regression of many intrapulmonary lymph nodules and tracheobronchial lymph nodes draining both lungs considerably complicated the histological analysis, especially that of the old lesions of first infection.

Of particular interest is the finding of unusually marked hemorrhagic myositis,

in location and in its histological picture representing marked degree of the well known Zenker degeneration of the recti muscles. Although not mentioned as a known complication of miliary tuberculosis in our leading text-books of pathology, this toxic Zenker degeneration has been known to occur in miliary tuberculosis (9).

*Case 4:* (B. G. H. 5453) Seventy-two year old white male. Cause of death: miliary tuberculosis and tuberculous meningitis. (Plates 6 and 7)

There is a typical firmly stony complex with a lentil-sized primary focus near the base of the left lower lobe which is firmly adherent to the diaphragmatic pleura, showing irregular, localized calcification just below the focus with firmly calcified-stony changes in the regional bronchopulmonary lymph nodes between left upper and lower lobe. The interlobar space and the entire pleural space around the left lung are completely obliterated by firm adhesions. The exogenous reinfection lesions are in the immediate subapical area of the right upper lobe, consisting of a few hazelnut-sized, firmly caseated nodules and one small hazelnut-sized cavity, with the wall in the medial part irregular and thin, 1 cm. underneath the mediastinal surface. There is typical localized intrabronchial spread at and below the level of these lesions, with several cherry-sized, ill defined, recent tuberculous lobular pneumonic nodules with slight caseation, extending to the lower part of the right upper and the upper part of the right lower lobe. There is an additional recent lobular pneumonic tuberculous lesion, somewhat wedge-shaped, in the lateral basal portions of the left lower lobe. A few lymph nodes in the anterior mediastinum regional to the right upper lobe, one paratracheal node and one lymph node in the right venous angle show complete, more or less firm caseation, with minimal chalky material in the lymph node of the venous angle. All remaining lymph nodes regional to the right lung, including the interlobar, bronchopulmonary and the upper and lower tracheobronchial groups, show grossly very firm anthracosis but no tuberculous lesions. The pulmonary tissue between the caseated lesions in the right subapical area is slightly indurated. The left apex and subapical area are entirely free of scars or older fibrocaseous lesions. All lobes contain many rather densely sown miliary tubercles.

There is distinct hematogenous tuberculosis of both kidneys with small tuberculous abscesses of the so-called excretion type, especially in the pyramids of the right kidney, with tuberculous infiltrations irregularly scattered over each cortex. There are but few scattered hematogenous tubercles in the liver.

Dissection of the brain was restricted, but clinical symptoms and cytological findings of the spinal fluid pointed strongly to tuberculous meningitis. Tubercle bacilli were not looked for in the spinal fluid. Smears taken from the subapical cavity showed innumerable tubercle bacilli.

Plates 6 and 7 show the lesions of the primary complex and some of the changes brought about by exogenous reinfection. The histological examination in this case was as complete as possible, including the entire primary complex, the reinfection lesions from the right upper lobe with the cavity and the surrounding tissue with many firm caseated tubercles, and all lymph nodes regional to the right upper lobe, including all bronchomediastinal groups and the nodes in the right venous angle; also various parts of lung tissue from lower and lateral portion of the right upper, the right lower, the right middle, with all lymph nodes regional to these lobes, and lung tissue from the apex of the left upper and different parts from the left upper and left lower lobe, including especially those areas with typical recent changes of hemorrhagic acinous tuberculosis, and various sections from portions of grossly typical miliary tuberculosis. Finally, all lymph nodes regional to the left lung, extending to the venous angle, were examined.



PLATE 6

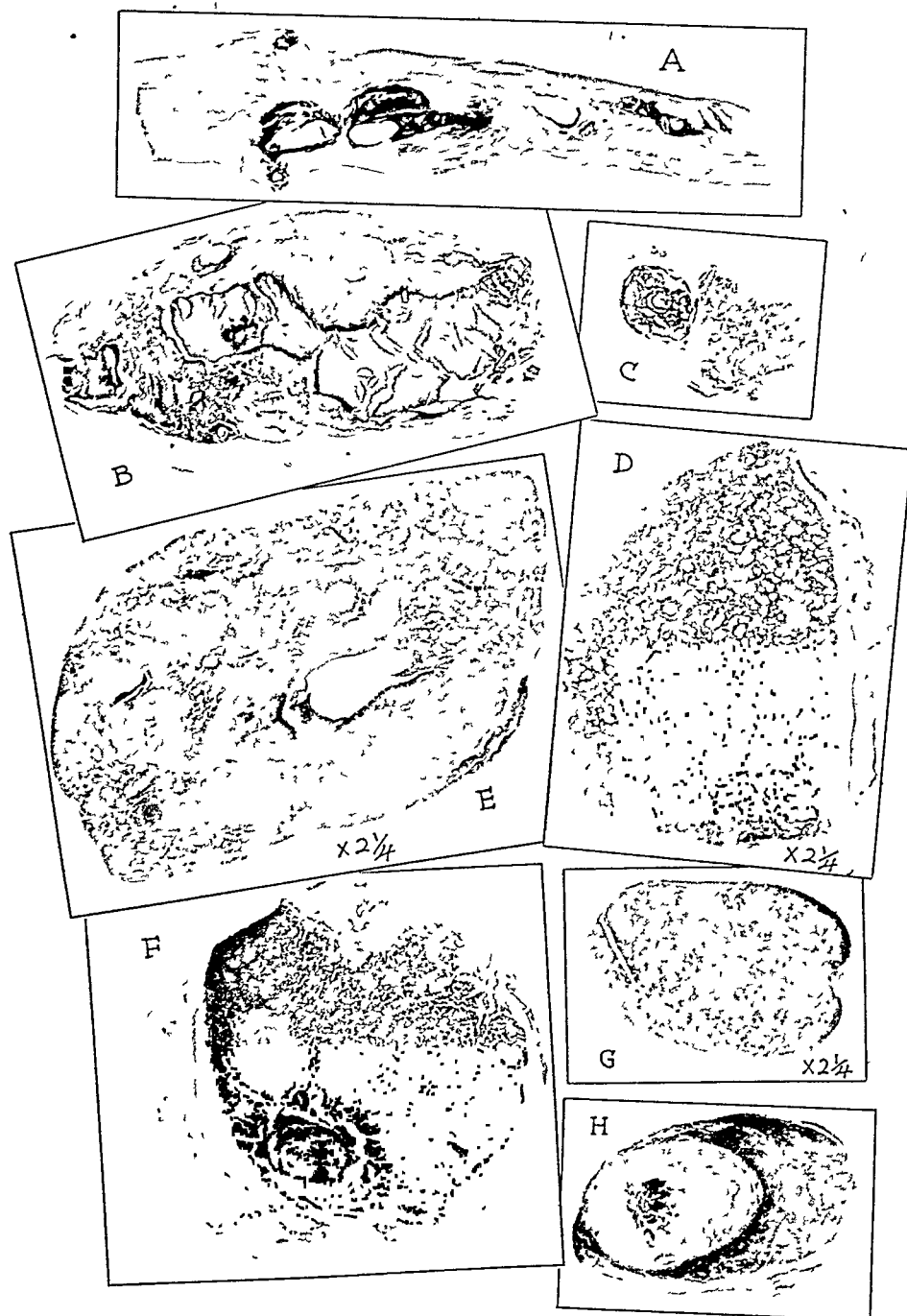


PLATE 7



*Histological findings:* The lesions forming the primary complex are histologically typical in every respect. C, B and A on plate 7 show the microphotographs of the small primary focus in a firm, stony state, surrounded by a thin bony shell (C), the large calcified stones with localized bone formation and some loose lymphoid marrow in one bronchopulmonary lymph node (B), and the irregular, elongated stone formation in the diaphragmatic pleura (A). In a few other lymph nodes of the left bronchopulmonary group there is, in addition to firm calcification, also localized anthracosilicosis. Photograph E shows a typical picture of a tuberculous cavity with unusually massive caseated detritus lining its wall which is still in process of active disintegration. The cavity is surrounded by many large bronchial tubercles. The entire picture appears typical for a massive localized intra- and peribronchial spread. In other sections a few small hyalinized scars could be seen between the large caseated foci. The bronchi around this area are in part compressed, filled with mucoid secretion, leucocytes and fibrocytes, apparently presenting small bronchiectatic cavities. In others with a similar content the entire wall is transformed into active tuberculous granulation tissue. Many of them in the areas of most recent massive intra-bronchial progression are filled with caseated or semifluid exudate, with the epithelial lining here and there still preserved. The presence of a few small interstitial tubercles, possibly of hematogenous origin, further complicates the picture. In some subapical areas distal to a few large intrabronchial tubercles, there is considerable atelectasis with fibrous induration. Old tuberculous lesions, including calcified or even hyalinized tubercles, are not seen, however, in these sections. The X-ray photograph does not show any evidence of chalky or calcified changes in this entire field. The lymph nodes around the bronchus draining the right upper lobe show firm anthracosilicosis but neither old hyalinized nor recent tubercles. Only in the right upper tracheobronchial lymph nodes is, apart from extensive anthracosilicosis, a rare hyalinized tubercle seen, and a small hyalinized structure including some chalky matter fragmented into small granules. This, we feel, is a tuberculous change. In other lymph nodes regional to the right upper lobe, including paratracheal and anteromediastinal groups, there is irregular and rather considerable hyalinization of the reticulum along with a few typical older hyaline small tubercles. The mediastinal lymph nodes are studded with many small recent epithelioid cell tubercles. The lymph node in the right venous angle contains a large, firmly caseated conglomerate tubercle, already distinctly encapsulated, with some chalky-hyalinized material in its centre. The remainder of the lymphoid tissue of this node contains several epithelioid cell tubercles. There is considerable tuberculous hyperplasia with recent central necrosis in a few other lymph nodes of the anterior mediastinum. In all lymph nodes surrounding the main bronchus of the right lung only excessive anthracotic induration could be found; hyalinized tubercles could not clearly be identified.

Photograph J (plate 6) shows a section through the right upper lobe near the area of the cavity (E, plate 7). F shows a section through an anterior mediastinal lymph node with large conglomerate and small recent epithelioid cell tubercles. H is a section through the lymph node in the right venous angle, with a firmly encapsulated, caseated-chalky tuberculous nodule, and G, a fairly diffusely tuberculous hyperplastic lymph node close to the right upper lobe in the anterior mediastinal group. D shows a fairly dense distribution of miliary tubercles and small conglomerate tubercles as found throughout both lungs, this section being taken from the left lower lobe. In sections taken from the right lower lobe adjoining the right upper there is recent tuberculous pneumonia of almost lobar type, with a picture suggestive of gelatinous pneumonia, and unusually marked hemorrhages into several alveoli with considerable amounts of fibrinous exudate. This entire picture, surrounded by scattered and conglomerate tubercles, represents a very early phase of acute

tuberculous pneumonia. In all the other parts of the right lung, especially in the remaining portions of the right upper lobes, the sections show various combinations of peribronchial tubercles and miliary tubercles of distinctly interstitial location. In sections from the right middle lobe and from both lobes of the left lung the picture is almost exclusively that of dense miliary tuberculosis with some of the miliary tubercles involving small bronchioli. In the lymph nodes regional to the left upper lobe there is only extensive anthracosis with considerable softening, while in the lymph nodes draining the left lower lobe there are, in addition, a few recent epithelioid cell tubercles.

*Epicrisis:* This, we believe, is a typical case of progressive reinfection in the presence of an old, entirely petrified complex with a somewhat unusual ossified pleural tubercle above the diaphragm close to the otherwise typical obsolete primary focus, and with firm, in part ossified, stones in the regional bronchopulmonary lymph nodes. In the area of the exogenous reinfection there are a few scars from obturation atelectasis, especially in the apical portion above and lateral to the recent cavitation and the nodular fibrocased tubercles. The contiguous intrabronchial extension is rather typical and quite massive, involving almost the entire right upper lobe and the adjoining upper area of the right lower lobe. In a few lymph nodes regional to the right upper lobe, including in particular one lymph node in the right venous angle, there are older fibrocased and in part hyalinized conglomerate tubercles with minimal chalky change. There was only one minute chalky particle, perhaps slightly calcified, in one right upper tracheobronchial lymph node included within an older fibrous, conglomerate tubercle. Neither grossly, histologically, nor especially roentgenologically was there any trace of petrified lesions throughout the entire right lung and the regional lymph nodes. This progressive reinfection resulted in overwhelming miliary tuberculosis in both lungs and particularly in the kidneys. Secondary lymphogenous progression of very recent nature to the mediastinal lymph nodes was unusually marked in this case. This finding prevents any decision of the question whether or not the fibrocased lymph node changes regional to the right upper lobe had led to a so-called endogenous exacerbation within these lymph nodes. Inasmuch as in the lymph nodes regional to the left lung recent epithelioid cell tubercles were found, in no way different from the epithelioid cell tubercles surrounding the older fibrous-chalky conglomerate tubercles in the right angulus lymph node, it seems more likely to us that all these recent changes of lymph node tuberculosis, grossly and histologically corresponding to so-called tuberculous hyperplasia, have been caused by recent progression in connection with the overwhelming miliary tuberculosis. This, however, could be secondary only to the progressive reinfection in the right lung, as all the other lesions were of recent nature, conditioned by the overwhelming hematogenous spread. Again, as in the former cases, there was no evidence of a pathogenetic link between the very old obsolete primary complex and the anatomically typical progressive reinfection lesion involving apical and subapical areas of the right upper lobe.

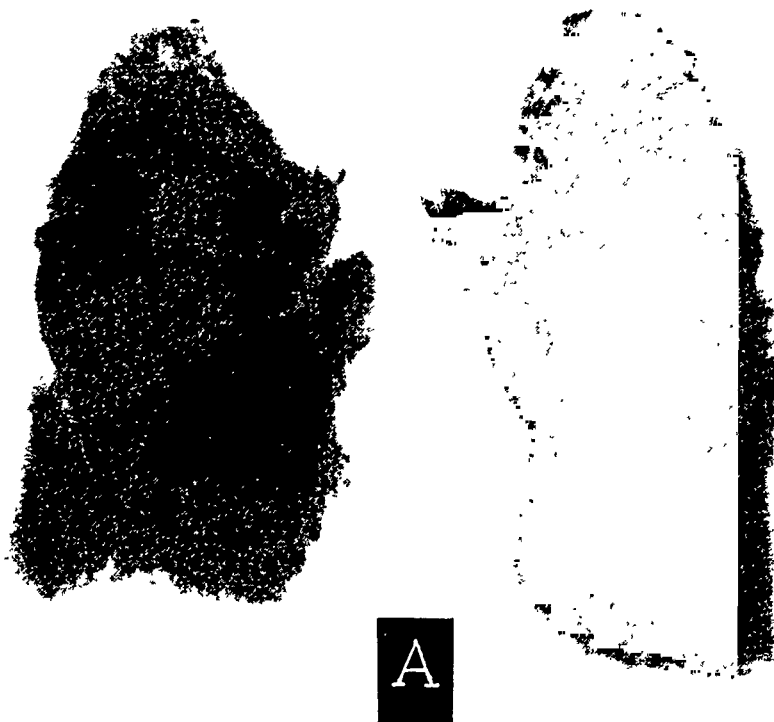
The history given in the patient's chart is as follows: He had worked in a flour mill steadily until two months previous to his death. There was distinct weight loss and complete anorexia for the last two months. He was observed for only a

few days in the hospital and the clinical diagnosis was virus pneumonia (?) with viral meningo-encephalitis. Most of the clinical symptoms pointed to distinct involvement of the leptomeninges (85 per cent lymphocytes, 15 per cent leucocytes; globulin ++, albumin ++). Tubercle bacilli were not looked for. There was also some blood in the urine. An X-ray examination, made with a portable machine, of the rapidly failing patient did not permit a diagnosis of tuberculosis. The marked weight loss and the anorexia were interpreted as a sign of a primary malignant lesion of the gastro-intestinal tract. Progressive subapical tuberculosis resulting in overwhelming miliary tuberculosis was not anticipated in this case.

*Case 5:* (B. G. H. 4888) Seventy-seven year old white female. Cause of death: Addison's disease from tuberculous destruction of both adrenal glands. (Plates 8 to 11)

Only a brief epicritic summary will be given of this case. There is fairly symmetrical, ossified apical and especially subapical tuberculosis of both upper lobes with firm calcification of a few left upper bronchopulmonary lymph nodes at the hilum of the upper lobe (plate 8, A), possibly pointing to the remnants of the old primary complex, a single parenchymatous lesion to which, however, cannot be recognized. Many apical and subapical lesions in both upper lobes are in firmly ossified state, containing a great deal of bone marrow (plate 9, C and D). In addition, there are in both upper lobes a few intrapulmonary lymph nodules with distinct bone formation around some central chalky-calcified detritus containing cholesterol crystals. It is impossible in this late state of ossification to determine whether there had been a real old primary complex, or whether the first infection directly had spread locally within the apical and subapical area or was followed by an early superinfection of these areas. No difference could be found in the structure and size of the various ossified subapical lesions in both upper lobes. In close relation, however, to these stony and ossified lesions there is found rather active caseated and cheesy-fibrous tuberculosis, particularly in the upper part of the right upper and in the midportion of the left upper and in the apical area of the right lower lobe (plate 8 B). The most striking finding among a large number of sections taken from both subapical areas is the presence of a stony cast within the lumen of a slightly dilated bronchus, apparently still in connection with the wall, but otherwise pointing in polypous fashion into the ectatic lumen (plate 10, E). In a few small areas contiguous to this firm stone which, in the elastic tissue stain readily betrays its original caseated nature, a few epithelioid cell tubercles with typical Langhans' giant cells can be recognized. Just about at the level of this tuberculous stone pointing into the contiguous ectatic bronchus, the mucosal lining of this bronchus is well preserved, although markedly inflamed in a mostly nonspecific papillary hypertrophic manner. There are distinct tuberculous changes with mostly hyaline-fibrous conglomerate tubercles in several anterior mediastinal and bronchopulmonary lymph nodes but no recent tuberculosis in any bronchomediastinal node. The hematogenous spread is here, for the most part, localized within the adrenals which show complete destruction by caseation. There are only a few recent caseated tubercles in the spleen and liver. The periaortic nodes and the retramediastinal lymph nodes regional to the adrenal glands show extensive caseation.

The histological examination in this case was most extensive, including practically all lesions found in both upper lobes and various hematogenous tubercles. Plate 9 shows several of the older and more recent tuberculous lesions from both subapical fields.



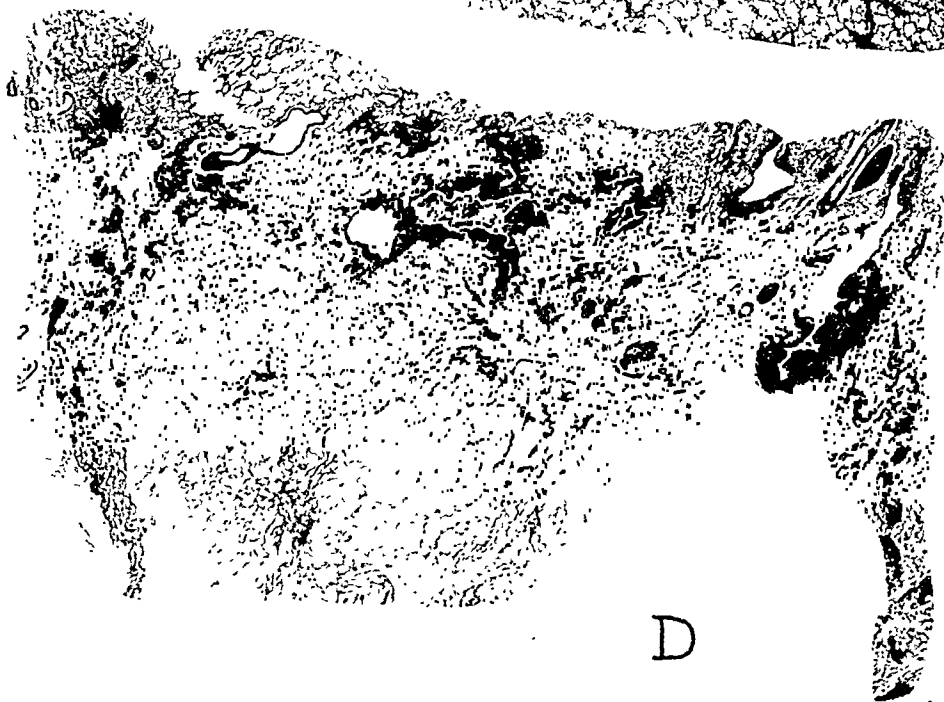
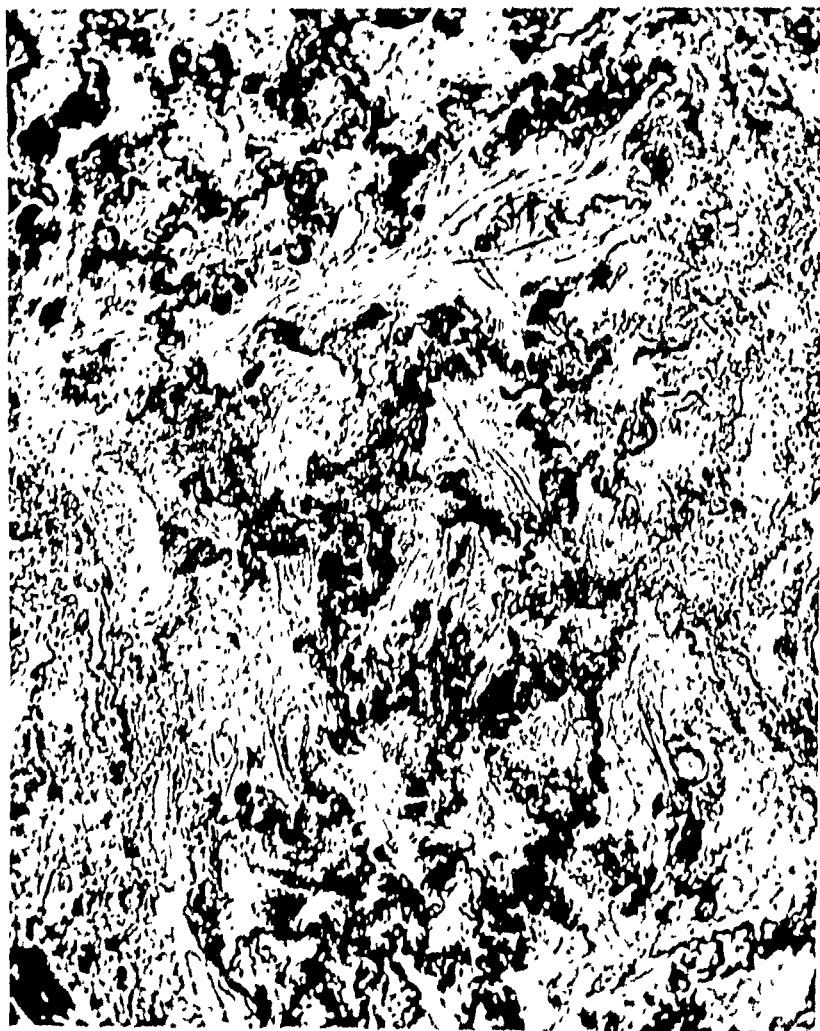


PLATE 9



F



E

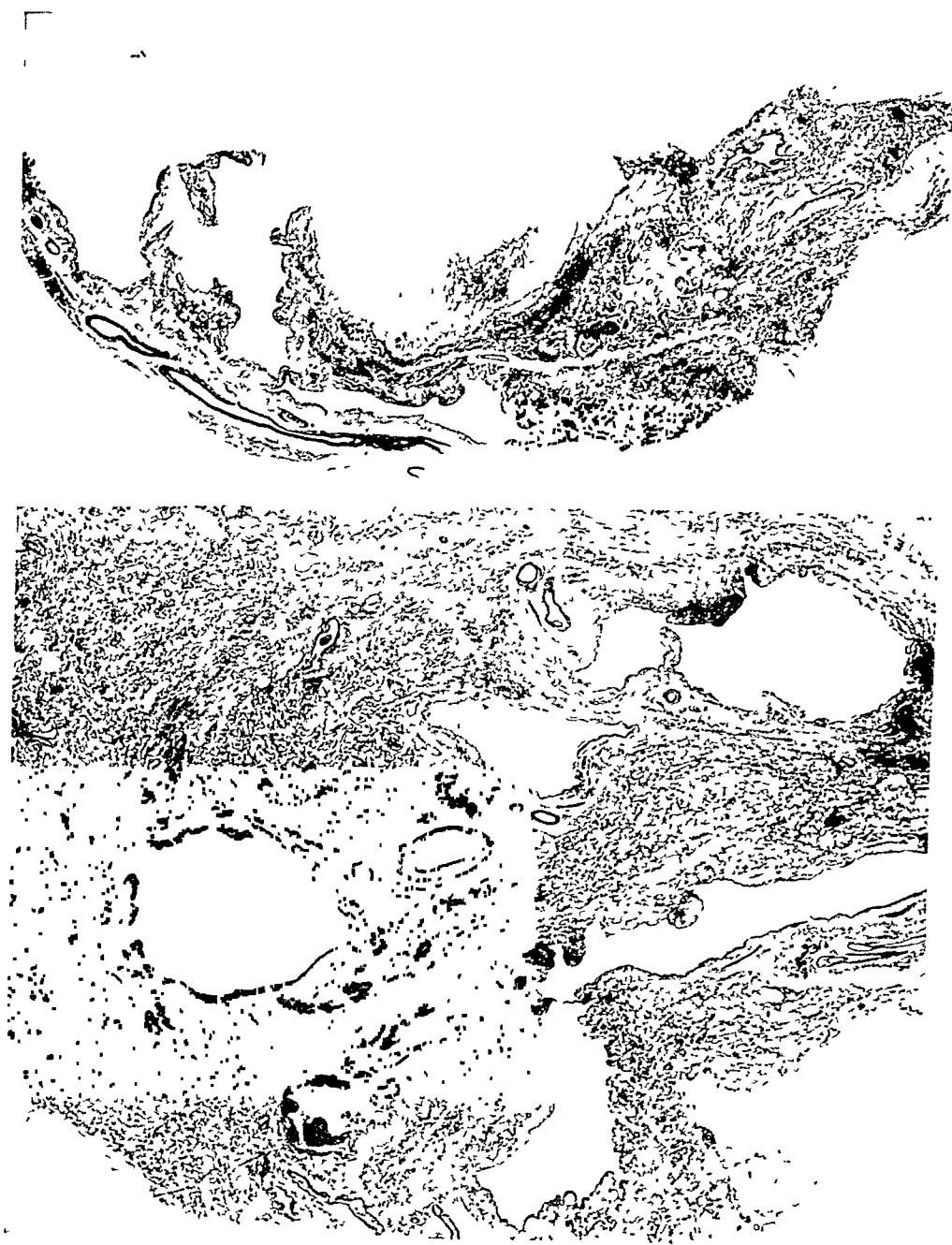


PLATE 11

This patient was known to have suffered from diabetes for the past twelve years. When admitted to the hospital on October 6, the symptoms of Addison's disease were already quite outspoken. The roentgenological diagnosis was old apical tuberculosis in both apices with active changes on the right side and in the left interscapular space. The patient died three and one-half weeks following admission.

The anatomical findings of the remaining 7 cases are given in condensed form in table 1. Some of these will be referred to in a summarized discussion of the entire group.

#### DISCUSSION

It is evident from our table that these various combinations of exogenous reinfection or superinfection with hematogenous tuberculosis occur in any age group. In this selected material the respective ages range from nineteen to thirty in 3 cases, from forty to fifty in 3 and from sixty to eighty in 5. In all 12 cases there were typical stony or ossified remnants of an old primary complex, including one case with firm calcification of mesenteric lymph nodes, pointing to an obsolete primary intestinal tuberculosis. In 4 instances there were two calcified or stony-ossified complexes, in 3 of these one in each lung, in the fourth one in each lobe of the left lung.

In one case (no. 2279) there was no complex formation, but only a single calcified-ossified parenchymatous focus, 1 mm. in diameter. In the other 10 cases with the typical remnants of an old primary pulmonary infection, the extent of the obsolete changes in the lymph nodes regional to the primary focus or foci varied considerably. In 3 instances only the nearest bronchopulmonary lymph nodes were involved, while in most of the others several regional lymph node groups were involved, in some of these rather diffusely.

Only in one of our cases, the last one discussed in some detail (table 1, no. 4888), the primary focus could not be identified. It was obscured among several old ossified-stony tubercles in one of the subapical areas. Firm calcification of a few bronchopulmonary lymph nodes regional to the left upper lobe, however, seemed to point to this lobe as the harbinger of the old primary lesion. There was no complex-formation regional to the right upper lobe, although several tubercles in the right apical and subapical area showed similar obsolete ossified or calcified structures as were seen in the left upper lobe. The presence of partly ossified intrapulmonary lymph nodules with anthracosilicotic changes in both subapical fields only added to an already complicated picture. In these late stages of structural regression with stone formation and ossification, it is impossible to determine the true relation between the typical remnants of an old primary complex and the various obsolete tubercles in such parts of the lungs which are tributary to the lymph nodes—with the obsolete primary complex changes: Gradually spreading primary infection by means of focal intrabronchial extension involving the opposite upper lobe, exogenous superinfection at or close to the time of the first infection, or true exogenous reinfection—any one of these three mechanisms could



have produced the final morphological picture as found postmortem in this case. With this one exception, the gross and microscopic distinction between the old primary complex and the postprimary reinfection lesions did not seem difficult, including a single instance (table 1, no. 4749) with two firmly calcified primary complexes, one on each side. The primary focus of the left-sided complex was within the subapical field, which was also the site of older localized chalky, fibrocaseous postprimary tuberculosis.

Location, anatomical type and extent of intrabronchial spread of the various reinfection lesions in our 12 cases are listed in the fifth column of the table. In 3 cases these reinfection lesions were restricted to one upper lobe; in one of these to the right subapical field (table 1, no. 4764); in the 2 others to the left subapical area (table 1, no. 5091 and no. 4749). In another case (table 1, no. 2279) only the right upper and right lower lobes, including the subapical area, were involved. This latter case was somewhat unusual. The site of the original reinfection lesions was not clear. There were several pea-sized fibrocaseous tubercles, the largest in the right subapical field, others, slightly smaller, in different parts of the right lower lobe; their gross and histological appearance was that of typical bronchial and peribronchitic tubercles with marked collateral hemorrhages. The left lung was free. Lymphogenous progression was very distinct, grossly involving all lymph nodes draining the right lower lobe. In the lymph nodes regional to the right upper lobe, however, there was no caseation but only small epithelioid and fibrous tubercles. It is possible that a true exogenous reinfection had produced several caseated tubercles first in the right lower lobe with typical reinfection complex changes in the regional lymph nodes and had extended by aspiration or additional superinfection to the right upper lobe. This is the same case in which the primary infection had restricted itself to a parenchymatous tubercle of 1 mm. diameter which was in firmly ossified-stony state.

Of the remaining 8 cases, in 5 the right upper lobe, in one the left upper lobe and in another the left lower lobe were the site of the most marked and apparently original and oldest reinfection lesions. But in all these cases there was more or less localized intrabronchial spread to other parts of the same lobe or lung and to some extent to the contralateral lung. There remains, then, only one case (table 1, no. 4888) in which the location of the reinfection lesions seemed fairly symmetrical in both upper lobes and their structure very similar.

Extent and severity of intrabronchial spread within the lungs was fairly marked in 5 cases involving both subapical fields and localized parts of one or both lower lobes (nos. 2181, 2596, 3364, 5453, 4051). In 2 cases it was comparatively moderate, involving only the left lower lobe in one (no. 2212) and the upper parts of both upper lobes in the other (no. 4888). In one case (no. 2425) which had been discussed at some detail there was considerable recent spread within both lungs.

The anatomical type of these reinfection lesions was largely similar to those presented in the preceding paper, consisting for the most part of chronic fibrocaseous tuberculosis or, in the few more recent lesions, of diffuse tuberculous bronchopneumonia. There were minimal chalky changes in 2 (nos. 2212 and 4051) and more mixed fibrous-chalky tuberculosis in one (no. 2596). Considerable

ossified-stony lesions, intimately combined with local fibrocaseous tuberculosis, were present in but one instance (no. 4888). There were cavities in 4 cases in all. Their location was in both upper lobes and in the left lower lobe (nos. 2596, 3364, 5453 and 4051).

Except for one case specifically discussed (no. 4764) there was lymphogenous progression from the reinfection lesions in every single instance. It was restricted to the side of the original reinfection lesion in 8 cases and bilateral in 3. In all these latter 3 instances there was actively progressing tuberculosis with extensive tuberculous pleuritis in one and with recent cavities in both lungs in the 2 others. The secondary lymph node tuberculosis was of the same character as the reinfection lesions, mostly fibrocaseous or occasionally fibrocaseous-chalky. The extent of the lymphogenous progression and the relatively slight (no. 4888) or very recent changes (no. 4051) in 2 cases of our series are indicated in the table.

So far, then, our pathogenetic analysis has shown that the cases in this series are not different from those in the preceding paper. In both groups there are, in every single case except one with a primary focus without lymph node changes, the typical remnants of an old primary complex and typical older or more recent postprimary reinfection lesions of mostly subapical location, with either locally restricted, moderate or sometimes more extensive intrabronchial spread. There is, however, a distinct quantitative difference in the degree of the intrabronchial spread of these reinfection lesions within the lung, insofar as extensive caseated ulcerative progression with massive involvement of large areas of both lungs was seen in several cases of the preceding group only. In other words, the typical picture of progressive bilateral phthisis was present in a few cases of the preceding series, while even progressive lesions with cavitations were more restricted, and intrabronchial extension in general less diffuse in the cases in this series. Also, lymphogenous progression from the lesions of reinfection was present in most of the cases included in both groups. The gross, topographic and structural analysis has proved, further, that the lesions of the old primary complex were of no genetic significance for the various results of the reinfections. The detailed analysis of 5 selected cases given above, and the study of the remaining 7 cases listed in the table indicate that the sources for the various hematogenous lesions found in all cases included in this paper were originally the pulmonary lesions brought about by exogenous super- or reinfection.

The hematogenous lesions are listed in the last column of the table. In 5 cases the picture of miliary tuberculosis of both lungs was present in addition to the older postprimary reinfection lesions previously discussed. In one of them (no. 3364) a very dense miliary spread had been brought about probably indirectly by deglutition tuberculosis of the intestinal tract, secondary to a few pulmonary cavities. This intracanalicular spread from the cavities led to extensive ulcerative tuberculosis of the intestinal tract, followed by massive caseation of the mesenteric lymph nodes, contiguously extending into the thoracic duct which was dissected *in toto*. Another possible source for hematogenous spread in this case was the recent tuberculosis of bronchomediastinal lymph nodes regional to the active cavernous pulmonary lesions with tuberculous bronchitis.

Of the other 4 cases with miliary tuberculosis of the lungs, there was in 3 (nos. 5091, 5453 and 4051) marked, acutely progressive acinous tuberculosis with fairly recent cavities, in one of these with hemorrhages in the walls of the cavities. In all these 3 cases there was recent lymphogenous tuberculosis in bronchomedias-tinal lymph node groups regional to the progressive pulmonary reinfection lesions. In the fourth case, however, the massive miliary tuberculosis in the lungs appeared related to recent conglomerate tubercles in a few paratracheal lymph nodes regional to localized chalky-fibrous tuberculosis within one subapical field. In this case alone, the anatomical-histological analysis was suggestive of lymphogenous-endogenous exacerbation or delayed lymphogenous progression, in the absence of intrabronchial progression of a chronic chalky-fibrous postprimary lesion entirely restricted to the left subapical area. The obsolete lesions of the primary complexes with the lymph node changes in a firmly petrified state appeared in no way related to this active lymph node tuberculosis which was found in the left lower paratracheal lymph nodes only.

A few scattered small miliary tubercles in the lungs, apparently of hematogenous nature, were found incidentally in 2 additional cases (nos. 2212 and 2279), together with hematogenous tubercles in various organs. In both there was extensive caseated lymphogenous progression from the postprimary pulmonary reinfection lesions, in one of them combined with older and recent tuberculous pleuritis, pericarditis and peritonitis. The number of hematogenous tubercles was, however, comparatively small in these 2 cases, not only in the lungs but also in such organs as liver, spleen and kidneys.

Our table clearly shows that in most cases of our series there were hematogenous tubercles in the liver, spleen and kidneys. These tubercles were easily seen with the naked eye, and especially in the 5 cases with overwhelming miliary tuberculosis, previously discussed, these organs showed considerable involvement. Tuberculosis of the spine with paravertebral abscesses, combined with many tubercles in liver, spleen, adrenals, kidneys and with caseation of the prostate, was present in only one case of this series (no. 2181). There were no hematogenous tubercles in the lungs in this case. All hematogenous lesions, including a few liver tubercles already calcified, appeared as metastatic lesions from a fairly massive fibrocaceous subapical tuberculosis of the lungs with a few cavities and distinct lymphogenous progression to the regional tracheobronchial lymph nodes. Other organs involved in various cases of this series included the suprarenals in 3 instances, the pancreas in one, the prostate in 3, the bladder in one, the brain in 2 and the leptomeninges in 4. Tuberculous leptomeningitis was the ultimate cause of death in these 4 cases. In one of these (no. 2596) there was chronic fibrocaceous tuberculosis of one kidney (the other had been removed surgically two years previous to death), the prostate and the bladder; in the other (no. 5453) there were small tuberculous abscesses in both kidneys. In the 2 remaining cases, the actively spreading reinfection in the lungs was the only possible source for tuberculous meningitis. The two small tuberculomata in the cerebellum and in the oblongated medulla which were found in one of these cases

(no. 4051) did not communicate with the ventricles nor with the subarachnoid space. Both tuberculomata were examined histologically. Finally, in one of our cases (no. 2279) a large tuberculoma of the pons was found, together with scattered hematogenous tubercles in both lungs, kidneys, liver, spleen and prostate.

A few older tuberculous ulcers were incidentally found in only 2 cases, in the colon (no. 2181) and in the lower ileum (no. 2279) with localized lymphogenous progression to one or more mesenteric lymph nodes.

The tabulation of the hematogenous lesions shows that there was in some cases considerable lymphogenous progression secondary to the blood-borne metastases or to the ulcerated lesions in the intestinal tract which had been apparently caused by intracanalicular spread from the pulmonary lesions. This lymph node tuberculosis was especially pronounced in the case of tuberculous serositis, with all bronchomediastinal, supradiaphragmatic, mesenteric, celiac, peripancreatic and periaortic lymph nodes involved. In 3 other cases the periportal, peripancreatic and periaortic lymph nodes showed recent caseated tubercles, apparently secondary to hematogenous tuberculosis in the liver, spleen or adrenals. Recent microscopic epithelioid cell tubercles were also present in bronchomediastinal lymph nodes regional to both lungs in cases with acute overwhelming miliary tuberculosis.

Supplementary to the table, a few clinical notes will be added, except to the 5 cases already discussed in the text:

*No. 2181:* All clinical symptoms pointed to a destructive lesion of the spine; roentgenologically, a markedly increased density was seen throughout both lungs with an increased hilar shadow and clouded apices. The clinical impression leaned towards a malignant metastatic tumor of the mediastinum or the lungs, and a malignant lesion of the spine, also possibly of metastatic nature.

*No. 2212:* This was an outpatient who had been in progressively failing health for several months. There was a history of syphilitic infection. At no time was it known that the patient had tuberculosis.

*No. 2279:* All clinical symptoms which had started five months previous to death pointed to a brain tumor. The chest was clear on physical examination; no X-ray photograph was taken of the lungs. The patient died following surgical ventriculography.

*No. 2596:* Two years previous to death, the left tuberculous kidney had been surgically removed. There was no history of any illness since, until three weeks previous to admission. Subjective and objective symptoms at this time were those of tuberculous meningitis. There were distinct physical findings in the left chest. An X-ray photograph of the lungs was not taken. The clinical diagnosis was tuberculous meningitis with active tuberculosis of the lungs. (From the anatomical picture it seemed most likely that the chronic fibrous-chalky-ulcerative tuberculosis of the left upper lobe had preceded the tuberculous infection of the kidney which had been removed two years previous to death. The primary complex in this case was in a completely obsolete, ossified state.)

*No. 3364:* This patient was a diabetic, although it was known that he had been treated for tuberculosis one year previous to death. Tubercle bacilli had never been recovered. The rapid progression of cavernous pulmonary tuberculosis with intracanalicular spread to the intestinal tract and consecutive massive caseation of the mesenteric lymph nodes and thoracic duct, leading to overwhelming miliary tuberculosis, was apparently entirely masked by the prominent symptoms of his diabetes.

*No. 4749:* Four years previous to admission there was an aphasic attack caused by cerebral arteriosclerosis. There was considerable weight loss during the last year. For the past four weeks the patient was growing progressively weak. There was no cough. Physical examination revealed harsh bronchovesicular breathing. He had shaking chills. The bedside X-ray film was diagnostic of miliary tuberculosis.

*No. 4051:* The patient was admitted on November 12, 1938. He had suffered from a cold in August of that year and had lost 15 pounds since. During the last seven days he had continuous headache. At the time of admission, the dominating symptoms were those of tuberculous meningitis. He died on the 29th of November.

The brief notes taken from the charts reveal that only in 3 cases the presence of chronic tuberculosis had been known clinically for some time. In the majority, however, symptoms of tuberculous meningitis or the fully developed picture of miliary tuberculosis, recognized only shortly before death, were the first and entirely dominating clinical manifestations of the tuberculous reinfections in their terminal state. Still in a few others, the true nature of the disease was not recognized until postmortem.

Chronic hematogenous tuberculosis appeared as the cause of death in 2 cases, tuberculous serositis including the pericardium in one, overwhelming miliary tuberculosis in 4, tuberculous meningitis in at least 3 (but possibly 5), tuberculoma of the brain in one, and Addison's disease in one. In not a single case, then, was death ultimately caused by the chronic pulmonary tuberculous process alone. There was no diffuse phthisic destruction. Only by further lymphohematogenous spread of the disease from the pulmonary reinfection lesions was the fatal termination brought about in various direct or indirect ways, and in a highly individual manner in every single case.

Schuermann concluded, from his postmortem studies of chronic pulmonary and of generalized hematogenous tuberculosis, that there is a reversed relationship between chronic phthisis and acute, generalized miliary tuberculosis. Our anatomical findings, though largely supporting his views, have revealed that exceptions might occur to the rule that these two types of tuberculosis are exclusive of each other. In one of our cases, acute intrabronchial progression affected a large part of the right lung in connection with a cavity. In the other, there were two moderate sized cavities, one in each lung, with recent intrabronchial spread within the lobe which contained the larger cavity (5 x 4 cm.). Yet, the typical picture of miliary tuberculosis of the lungs was present in both. It might be of interest in this connection that one of these observations concerned a senile male, seventy-two years of age, who had been in rapidly failing state, suffering from

extreme anorexia and considerable weight loss for two months preceding the first objective findings of hematogenous tuberculosis. In the other case, with pulmonary tuberculosis recognized one year previous to death, the complication of possible significance, in the conversion of a massive intracanalicular spread to the intestine into overwhelming miliary tuberculosis via the caseated mesenteric lymph nodes and thoracic duct, was severe diabetes.

Our analysis indicates that hematogenous generalization can occur in older age groups. It was found in 3 cases in the seventh and eighth decade of life. In regard to the tubercles or tuberculomata in the brain substance, our few observations show that such hematogenous brain lesions are not necessarily "directly or indirectly associated with primary tuberculosis" as Gesell and Uehlinger have claimed (10). In our 2 observations from this group and in an additional case included in one of the preceding papers (XIV) these tuberculomata were hematogenous metastases from exogenous super- or reinfection lesions.

The histological analysis of all those lesions which, in the roentgenogram, usually appeared as well circumscribed, calcified structures has revealed the presence of many anthracosilicotic, intrapulmonary and subpleural lymph nodules and considerable anthracosilicosis in bronchopulmonary lymph nodes. The X-ray photograph of one of our cases (no. 5091) is a good example of this complication. Similar nodules were also seen in case 2181 (table 1). It is intended to present in one of the forthcoming papers, dealing exclusively with the roentgenological appearance of various calcified structures of nontuberculous nature, the practical, morphological-diagnostic implication of these anthracosilicotic nodules, as seen especially in roentgenograms of the lungs taken postmortem. At this time, we only wish to say that histological analysis of intrapulmonary foci, in size, location and in their X-ray opacity indistinguishable from typical calcified tubercles, frequently proved their pure anthracosilicotic nature. The formation of compact, stony-ossified tubercles in areas containing anthracosilicotic stones is a reliable criterion of relative age, only insofar as the stone formation in these tuberculous lesions must have preceded the anthracosilicotic infiltration.

Of other features of histological interest, the intimate combination of nonspecific, chronic inflammatory changes with chronic tuberculous lesions deserves some comment. Histological analysis of both subapical areas in one of our cases (no. 4888) showed a large number of bronchiectatic cavities with retained mucoid secretion and considerable degree of hypertrophic papillary bronchitis (plate 11). There was the typical picture of collapse-induration between these ectatic bronchi, with unusually impressive contraction and thickening of the elastic membranes (plate 10, F), and, in close topographic relation, old, stony and ossified tubercles occluding small order bronchi (plate 10, E). The walls of these cavities, although some of them seemed to communicate with tuberculous bronchi, appeared frequently of an entirely nonspecific structure. It seemed as if their formation was conditioned in part by the indurative pneumonitic processes within the intervening parenchymatous remnants. Similar endarteritic changes, as described in atelectatic areas in 2 cases of the preceding paper, were seen also in this case in the midst of typical scars from collapse-induration.

## SUMMARY

The anatomical findings in 12 cases of pulmonary reinfection lesions combined with various forms of hematogenous tuberculosis are presented. Their age range is between nineteen and seventy-five years, with 5 older than sixty years. Detailed histological analyses, supplemented by charts, X-ray and microphotographs, are given in 5 cases of the series. The cause of death was not phthisic destruction of the lungs, but hematogenous tuberculosis in all, including overwhelming miliary tuberculosis in 4 (mostly in the older age group), tuberculous meningitis in at least 3, tuberculoma of the brain, tuberculosis of the spine, tuberculous destruction of the adrenal glands and tuberculous serositis. The various organs involved by hematogenous tuberculosis, the exogenous reinfection lesions in the lungs, and anatomical type and location of the primary complex are listed individually in a table.

The anatomical-histological analysis attempts to prove that the pulmonary super- or reinfection lesions, typical in their location and of characteristic structural type, had preceded the development of the various blood-borne metastases in every single instance. With one exception, there was anatomical evidence of lymphogenous progression to bronchomediastinal lymph nodes from the pulmonary reinfection lesions. In all cases except one there were obsolete remnants of a primary pulmonary or (in one instance only) intestinal complex. No trace of any possible pathogenetic link between the obsolete first infection and the usually chronic fibrocaseous super- or reinfection lesions could be found. In one case, with a known history of hematogenous tuberculosis of one kidney a few years previous to death, the anatomical picture, postmortem, pointed to a typical chronic apical and subapical tuberculosis as its source, and not to the firmly obsolete primary complex.

Of the cases with dense miliary tuberculosis of the lungs, the apical and subapical reinfection lesions showed more or less localized intrabronchial progression within the lungs as well as lymphogenous extension to the regional lymph nodes. In one instance the anatomical picture pointed to local active lymph node tuberculosis alone in a paratracheal group regional to a chronic apical reinfection lesion with no evidence of active intrabronchial progression. In another observation, overwhelming miliary tuberculosis was caused by massive caseation of mesenteric lymph nodes and of the thoracic duct, secondary to tuberculous ulceration of the intestine which, in turn, was caused by intracanalicular spread from two pulmonary cavities.

Other unusual features included an observation of tuberculous meningitis secondary to a recent exogenous reinfection restricted to one subapical area, in the absence of lymphogenous spread, and findings of acute Zenker degeneration of the recti muscles in a case of miliary tuberculosis. Also, the close interdependence of old apical and subapical tuberculosis with intrabronchial obstruction from chronic tuberculous processes with collapse-induration and chronic bronchiectasis with papillary bronchitis of nonspecific appearance is demonstrated on the basis of serial studies in one instance of ossified-calcified apical and subapical tuberculosis with but limited active progression. A few anatomical findings indi-

cate that chronic reinfection tuberculosis of the lung can culminate in acute overwhelming miliary tuberculosis. But even in these exceptions, the reinfection lesions were mostly localized to one or both apical and subapical areas, with no diffuse phthisic progression.

Brief abstracts are added from the clinical records, revealing that in 3 cases, only, the presence of chronic tuberculosis had been known for some time. In all the others, symptoms of tuberculous meningitis or of the fully developed picture of miliary tuberculosis, diagnosed only shortly before death, were the first manifestations of the disease, tuberculosis, while in a few others it was not recognized at all.

#### SUMARIO

Preséntanse los hallazgos anatómicos en 12 casos de lesiones pulmonares tipo reinfección combinadas con varias formas de tuberculosis hematógena. La edad de los enfermos variaba de diecinueve a setenta y cinco años, teniendo 5 más de sesenta. Para 5 casos de la serie ofrécese el análisis histológico pormenorizado complementado con gráficas, radiografías y microfotografías. La causa de la muerte no consistió en destrucción tísica de los pulmones, sino invariablemente en tuberculosis hematógena, comprendiendo una granulía agobiadora en 4 (la mayoría en el grupo de edad más avanzada), meningitis tuberculosa por lo menos en tres, tuberculoma del cerebro, tuberculosis raquídea, destrucción tuberculosa de las adrenales y serositis tuberculosa. En las tablas enuméranse por separado los varios órganos afectados por la tuberculosis hematógena, las lesiones de reinfección exógena en los pulmones y la forma anatómica y localización del complejo primario.

El análisis anatómico-histológico trata de demostrar que las lesiones pulmonares de super- o reinfección, típicas en su situación y de característico tipo histológico, habían precedido la aparición de las varias metástasis hematíferas en todos los casos. Con una excepción había signos anatómicos de evolución linfógena a los ganglios linfáticos broncomediastínicos desde las lesiones pulmonares de reinfección. En todos los casos menos uno había restos antiguos de un complejo pulmonar o (sólo en un caso) intestinal primario. No pudo descubrirse ningún indicio de posible enlace patogenético entre la infección primaria anticuada y las lesiones fibrocasadas de super- o reinfección en su mayoría crónicas. En un caso con historia conocida de tuberculosis hematógena de un riñón algunos años antes de la muerte, el cuadro anatómico en la autopsia señalaba como foco primario una típica tuberculosis apical y subapical crónica y no al complejo primario decididamente anticuado.

De los casos con granulía densa de los pulmones, las lesiones apical y subapical de reinfección indicaban agravación intrabronquial más o menos localizada, en los pulmones, así como difusión linfógena a los ganglios linfáticos regionales. En un caso el cuadro anatómico apuntaba a tuberculosis ganglionar activa local, exclusivamente en un grupo paratraqueal correspondiente a una lesión apical crónica de reinfección, sin signos de evolución intrabronquial activa. En otra observación la granulía agobiadora era producida por caseación masiva de los



ganglios linfáticos mesentéricos y del conducto torácico, secundaria a ulceración tuberculosa del intestino, la que a su vez se debía a propagación intracanalicular desde dos cavernas pulmonares.

Otras características extrañas comprendían una observación de meningitis tuberculosa secundaria a una reinfección exógena reciente limitada a una zona subapical en ausencia de propagación linfógena y hallazgos de degeneración de Zenker aguda de los músculos rectos en un caso de granulia. Igualmente quedó demostrada la íntima interdependencia de la antigua tuberculosis apical y subapical con obstrucción intrabronquial debida a procesos tuberculosos crónicos con la colapso-induración y bronquiectasia crónica con bronquitis papilar de aspecto anespecífico, tomando por base los estudios seriados en un caso de tuberculosis apical y subapical osificada-calcificada de limitada evolución. Algunos hallazgos anatómicos indican que la tuberculosis pulmonar crónica de reinfección puede culminar en granulia aguda agobiadora. Aun en esas excepciones las lesiones de reinfección estaban en su mayoría localizadas en una o ambas zonas apical y subapical sin evolución tísica difusa.

Agréganse a los protocolos clínicos breves sumarios, revelando que sólo en 3 casos había sido conocida por algún tiempo la presencia de tuberculosis crónica. En todos los demás, los síntomas de meningitis tuberculosa o el cuadro de una granulia en pleno desarrollo, diagnosticada poco antes de la muerte, constituyeron las primeras manifestaciones de la enfermedad, tuberculosis, mientras que en algunos otros no fué reconocida para nada.

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## *AMERICAN TRUDEAU SOCIETY*

### **Diagnostic Standards**

There seems to be general agreement that this standard work is in need of revision, so the appointment of a new committee to undertake this important assignment was authorized by the Executive Committee of the American Trudeau Society at its meeting on December 2, 1944.

All physicians using the present edition are requested to submit their suggestions as to sections which need revision and, better still, to indicate lines along which they think the revisions should proceed.

Comments should be sent to Dr. Cameron St. C. Guild, Executive Secretary of the American Trudeau Society, who will see that they are brought to the attention of the Committee on Revision of Diagnostic Standards. (Address: 1790 Broadway, New York 19, New York.)



# MINIMAL TUBERCULOUS LESIONS OF THE LUNG<sup>1</sup>

## *Their Clinical Significance.*

DAVID REISNER AND JEAN DOWNES

Case-finding measures for the detection of pulmonary tuberculosis in the asymptomatic stage have in recent years become recognized as one of the most important means in the control of the disease. Routine radiographic examinations of the chest of apparently healthy persons, with particular emphasis on those presenting a history of exposure to infection in the household, as well as mass surveys of selected groups of the general population, have been demonstrated as a sound and practical method of case-finding. More recently the scope of these activities has been expanded to an unprecedented scale because of the requirement of a routine preinduction chest roentgenogram of all selectees. In addition, case-finding programs are being carried out in increasing volume by official as well as private agencies, and there is reason to believe that the coming years will see further extension of such activities.

Experience indicates that, in a large proportion of the cases of tuberculosis discovered through such routine examinations, the extent of the lesion is within the limits of minimal stage, as defined in the Diagnostic Standards of the National Tuberculosis Association (1). Among household contacts to known cases of tuberculosis, 65 per cent of those showing radiographic findings indicative of the reinfection type of tuberculosis presented lesions of minimal extent (2). Of the cases discovered through mass surveys, approximately 70 per cent showed involvement which was considered within the limits of the minimal stage (3).

With the constantly expanding case-finding programs bringing to light large numbers of cases of tuberculosis not previously known, there has developed a definite need for determining criteria for the evaluation of the clinical significance of the minimal lesion. The principal question is the one concerning the potential and actual risk of progression of such lesions to advanced and manifest clinical disease. The important practical considerations which present themselves in this connection may be stated as follows: First, when should one regard the presence of minimal tuberculosis as an indication for treatment? This question must be considered in the light of the consequences that the institution of therapeutic measures often entails, such as cessation of the patient's normal activities and disruption of family life. Second, to what extent do persons showing such lesions represent a risk connected with normal employment? At present, the question as to acceptability for military service occupies a place of particular significance. Third, to what extent is there an indication for intensive and long-term supervision of the individual with a minimal tuberculous lesion, either by the private physician or by public health agencies?

That the early, usually asymptomatic, tuberculous lesion of minimal extent represents a frequent precursor of manifest and progressive disease, has in recent

<sup>1</sup> From the Bureau of Tuberculosis, New York City Department of Health and the Milbank Memorial Fund, New York, New York.

years been emphasized by a number of observers. However, in only a relatively small number of cases in which minimal pulmonary tuberculosis is found is it possible to determine its truly "early" character by noting the development of a recent lesion on serial roentgenograms taken at frequent intervals. At the present time intensive case-finding measures of this type, such as are being carried out in colleges, in nursing schools and, to some extent, in contacts to known cases of tuberculosis, are of necessity rather limited in volume.

Since in the great majority of the cases discovered on routine examination the pulmonary changes are present in the initial roentgenogram, it becomes necessary to evaluate their significance on the basis of the available data which, aside from the roentgenographic evidence of the lesion, are usually quite meagre. While the changes observed in the film may well conform to the standard definition of minimal tuberculosis, as far as their extent is concerned, yet within the established limits are included lesions of different types, which have dissimilar potentialities and clinical significance. In some cases the roentgenological appearance of the lesion is essentially identical with the one found in apparently recent infiltrates developing in the course of observation. Others exhibit findings indicative of varying degrees of anatomical healing and are, therefore, of questionable significance, while in still others the demonstrable changes present characteristics of old and apparently obsolete lesions.

The study to be reported here deals with the behavior of the minimal tuberculous lesion during the course of observation and was undertaken for the purpose of determining some of the significant factors related to the risk of development of progressive disease.

#### DESCRIPTION AND CLASSIFICATION OF MATERIAL

The material was collected from ambulatory chest clinics of the New York City Department of Health. The selection was made with a view of obtaining a random sample of cases representative of the clinic population. Only cases who had come under observation with the initial diagnosis of minimal pulmonary tuberculosis of the reinfection type were included in the study. In order to obviate, as far as possible, a one-sided selection, intensive efforts were made to obtain adequate follow-up information on the cases for whom clinic observation had been discontinued for a period of more than six months prior to completion of the study.

The material used for the final analysis consists of 469 persons, of whom 291 were white and 178 non-white, the latter consisting almost entirely of Negroes and Puerto Ricans. In the total sample there were 200 males and 269 females, the number of females exceeding that of the male group by about 35 per cent. Since analyses by sex showed no indication that females were more liable to progressive disease than males, the data for the two sexes have been combined. None of the patients was less than 10 years of age; 24 per cent were adolescents or young adults under 25 years of age; 58 per cent were in the age group between 25 and 44 years; and 18 per cent were 45 years of age or older.

In the majority of the cases the pulmonary lesions were discovered on routine

chest roentgenograms, taken either because of a history of contact, in the course of mass surveys or as part of routine preemployment examination. In 76 per cent of the total there were no significant subjective symptoms at the time of initial diagnosis. About 10 per cent gave a history of hemoptysis or blood-streaked sputum, 13 per cent had had some loss of weight and 11 per cent complained of unusual fatigue. No definite correlation could be found between the presence or absence of such symptoms and the character or presumed clinical significance of the lesion demonstrated on the roentgenogram. Other symptoms referable to the respiratory tract, such as chest pain, cough, expectoration and dyspnea, were even less reliable as an index for evaluation of the clinical importance of a given lesion. Not infrequently such complaints were found to be due to affections of the respiratory system apparently unrelated to the tuberculous changes, particularly in middle aged and elderly persons.

Since it has been the general experience that the physical examination rarely elicits abnormal findings in lesions of minimal extent, an analysis of such findings was omitted in the present material.

With the exception of a small number of cases the sputum was found to be negative for tubercle bacilli at the time of initial examination, the concentrated method having been used in most instances. It may be expected, however, that more intensive studies, such as repeated cultures and animal inoculations of the sputum or gastric contents, would in all probability demonstrate positive results in a considerable proportion of cases with minimal tuberculous involvement, as indicated by recent observations of Decker, Ordway and Medlar (4). Because of limited facilities these procedures could not be employed on a routine basis in this material. For similar reasons, other laboratory examinations, such as erythrocyte sedimentation rates and other blood studies, were not-carried out.

In ambulatory material of the type included in this study the roentgenological findings may be regarded as the most important single criterion for the determination of the clinical significance of the minimal tuberculous lesion. The changes observed on the roentgenogram at the time of initial examination were classified according to extent, location and character of the lesion.

As regards the extent of involvement, the following definition of minimal tuberculosis contained in the Diagnostic Standards of the National Tuberculosis Association was used as a basis: "Slight lesion without demonstrable excavation confined to a small part of one or both lungs. The total extent of the lesions, regardless of distribution, shall not exceed the equivalent of the volume of lung tissue which lies above the second chondrosternal junction and the spine of the 4th or body of the 5th thoracic vertebra on one side."

The location of the lesion was considered under three main categories, namely: apical, subapical and combined apical and subapical. These groups were further subdivided according to involvement of either the right or left lung or bilateral localization.

An attempt was made to express the character of the lesion as portrayed on the roentgenogram in terms of the presumed pathologico-anatomical changes. The lesions were classified according to their predominant features and divided



into four main types, namely: (1) exudative; (2) 'productive and fibrotic; (3) combined exudative-productive; (4) fibro-calcific. The following definitions of terms were set up as a guide:

(1) *Exudative*: Roentgenologically, the density usually shows rather ill-defined borders, occasionally it may be well circumscribed; it is "soft" in appearance, either round or irregular in shape. The size is variable, usually ranging from one to two or three centimeters in diameter. The individual lesion may represent either a single focus or it may be composed of several smaller confluent densities. The intensity of the shadow depends on the size of the lesion, it may be either homogeneous or flocculent in appearance (figure 1A).

The underlying pathological changes may be assumed to represent a pneumonic infiltration involving the parenchyma of the lung which may or may not have undergone caseation but has not progressed to obvious excavation. The area of involvement may range from a group of pulmonary acini to one or more lobules.

(2) *Productive and fibrotic*: From the roentgenological appearance a distinction may be made between two main forms, namely: (a) discrete nodular densities, usually multiple, of small size, showing well defined borders, "hard" in appearance, either round or irregular in shape; (b) strand-like or linear densities, sharply outlined, often irregular in shape and distribution. The majority of the cases included in this category present a combination of form *a* and *b* (figure 1B).

The pathological changes responsible for the roentgenological findings are assumed to be nodular foci, either of miliary or acinous type, consisting either of tuberculous granulation tissue or fibrosis or of a combination of both. An encapsulated caseous focus may also present a similar roentgenological appearance. The stringy or linear densities may be accounted for by formation of fibrous tissue arranged in strand-like fashion. Manifestations of anatomical healing may be considered as a distinct characteristic of lesions of this type.

(3) *Exudative-productive*: This form may be regarded as an intermediate group between the two preceding types, the roentgenological findings presenting a combination of the features of both the exudative and productive-fibrotic elements in varying proportions (figure 1C). The pathological findings in cases of this type would appear to be a combination of the essential tissue changes occurring in tuberculosis, namely, the exudative and productive form of reaction, associated with organization and healing.

(4) *Fibro-calcific form*: Roentgenologically, the changes consist of sharply defined nodular densities, showing either round or irregular borders. The nodules are usually multiple; their distribution is scattered; they are generally of small size, measuring several millimeters in diameter, only rarely exceeding one centimeter. The intensity of the shadows is of a type usually interpreted as characteristic of calcium deposition. Such findings often occur in combination with changes indicative of strand-like and linear fibrosis (figure 1D).

The underlying morbid changes may be assumed to consist of calcareous or cheesy-calcareous foci, usually occurring in combination with varying degrees of fibrosis. This type of lesion may be interpreted as an expression of an advanced phase of anatomical healing.

Table 1 shows the distribution of the 469 cases with minimal tuberculosis according to the predominant character of the lesion on initial diagnosis, separately for white and non-white patients. There were no important differences between the proportions of white and non-white persons in the individual categories of lesions; 47 per cent of the total showed lesions of the exudative or exudative-productive type; a little less than two-thirds of these had lesions of the exudative type. About one-third of the total cases, white and non-white, presented lesions classified as of a productive and fibrotic type, and from 14 to 20 per cent exhibited changes of a fibro-calcific character.

An evaluation of the behavior of the minimal tuberculous lesion requires observation for a considerable period of time after initial diagnosis. In the present material the shortest period of observation was limited to two years, excepting cases dying within that period, and the longest period of observation was fifteen years. Sixteen cases, or 3.7 per cent of the total, were observed for a period of only two years; 50 per cent of the cases were observed five years; 17 per cent

TABLE 1

*Distribution of cases of minimal tuberculosis by color of patient and character of lesion*

CHARACTER OF LESION ON FIRST DIAGNOSIS OF TUBERCULOSIS	PER CENT		NUMBER	
	White	Non-white	White	Non-white
Total cases.....	100.0	100.0	291	178
Exudative.....	29.6	30.3	86	54
Exudative-productive.....	17.5	16.3	51	29
Productive and fibrotic.....	33.3	39.9	97	71
Fibro-calcific.....	19.6	13.5	57	24

were observed as long as seven years; and 18 cases, or 4 per cent, were observed ten years or longer. For the most part the analysis of the material will be limited to a five-year period of observation.

The behavior of the lesion was determined by means of serial roentgenographic studies during the follow-up period and was classified into four main types, namely: frankly progressive, unstable, regressive with subsequent stabilization, and stationary, according to the following definitions:

(1) *Frankly progressive*: The lesion shows frank increase in extent of involvement, usually into a more advanced stage of the disease; development of demonstrable cavity is to be considered as a most important evidence of progression.

(2) *Unstable*: The lesion shows slight progression alternating with regression, or vice versa, without causing obvious extension of the disease process, but at the same time lacking clear-cut evidence of stability.

(3) *Regressive*: Regression may take place either by complete or partial absorption of the lesion, by organization with fibrosis, by calcification or by combination of any of these modes of healing. Generally speaking, regression may be considered as an indication of favorable behavior of the lesion. As long as



FIG. 1. Roentgenograms demonstrating types of lesions in minimal tuberculosis:  
A: Predominantly exudative infiltrate in left first anterior interspace.  
B: Productive-fibrotic lesion in left apex, consisting of "hard" nodules and fibrotic strands.



Fig. 1—*Continued*

C: Exudative-<sup>stands</sup>productive lesion in right apex consisting of an area of "soft" infiltration in combination with dense fibrous strands

D: Fibro-calcific lesion involving the left apex.

the process of regression continues, the lesion has to be regarded, from an anatomical standpoint, as active.

(4) *Stationary*: The lesion shows no change in extent or character during the period of observation.

ANALYSIS OF MATERIAL

*Risk of progressive disease and mortality in relation to character of lesion*: The risk of progression of disease for cases of minimal pulmonary tuberculosis can be most precisely arrived at by the use of a simplified method of life-table analysis. The population base may be expressed as units of time or years of observation

TABLE 2

*Per cent of cases of minimal tuberculosis showing no progression of disease during five years after initial diagnosis of tuberculosis (white persons)*

YEARS AFTER DIAGNOSIS	AVERAGE NUMBER OF PERSONS AT RISK	NUMBER WITH PROGRESSIVE DISEASE	PERCENTAGE WITH PROGRESSIVE DISEASE	PERCENTAGE WITH NO PROGRESSIVE DISEASE	PERCENTAGE WITH NO PROGRESSIVE DISEASE THROUGH PAST AND SELECTED YEARS
	Exudative or exudative-productive lesions				
1	137	45	32.8	67.2	67.2
2	92	5	5.4	94.6	63.6
3	85	7	8.2	91.8	58.4
4	61	4	6.6	93.4	54.5
5	33	2	6.1	93.9	51.2
	Productive and fibrotic, or fibro-calcific lesions				
1	154	5	3.2	96.8	96.8
2	149	0	0	100.0	96.8
3	144	2	1.4	98.6	95.4
4	109	1	0.9	99.1	94.5
5	69	0	0	100.0	94.5

for each individual after the initial diagnosis. This method is convenient for use where the periods of continuous observation vary and has been applied to the data of this study.<sup>2</sup>

Tables 2 and 3 show the percentage of cases with no progression of disease during five years after the initial diagnosis of tuberculosis. These data are presented graphically in chart 1. The cases are classified according to color of patient and character of the lesion. Patients with productive and fibrotic lesions and those with fibro-calcific lesions have been combined into one group for comparison with patients showing lesions of an exudative or exudative-productive character. It is evident that the risk of progression of disease was very much greater for patients showing roentgenographic evidence of a presumably early

<sup>2</sup> It should be pointed out that patients showing progressive disease cease to be a part of the population after progression has been noted.

lesion, exudative in character, than it was for patients with lesions showing indications of anatomical healing at the time of initial diagnosis. At the end of five years only 51 per cent of the white and 39 per cent of the non-white patients with lesions of exudative or exudative-productive type had shown either regression of the lesion with subsequent stabilization or stability throughout the observation period. Conversely, 49 per cent of the white and 61 per cent of the non-white patients showed some evidence of progression during the period of observation.

Relatively few of the patients with productive and fibrotic and of those with fibro-calcific lesions showed progression or instability of the lesion; at the end of five years' observation the proportions were 5 per cent of the white and 14 per

TABLE 3

*Per cent of cases of minimal tuberculosis showing no progression of disease during five years after initial diagnosis of tuberculosis (non-white persons)*

YEARS AFTER DIAGNOSIS	AVERAGE NUMBER OF PERSONS AT RISK	NUMBER WITH PROGRESSIVE DISEASE	PERCENTAGE WITH PROGRESSIVE DISEASE	PERCENTAGE WITH NO PROGRESSIVE DISEASE	PERCENTAGE WITH NO PROGRESSIVE DISEASE THROUGH PAST AND SELECTED YEARS
Exudative or exudative-productive lesions					
1	83	41	49.4	50.6	50.6
2	42	3	7.1	92.9	47.0
3	39	3	7.6	92.4	43.4
4	33	2	6.1	93.9	40.8
5	18	1	5.6	94.4	38.5
Productive and fibrotic, or fibro-calcific lesions					
1	95	7	7.4	92.6	92.6
2	88	0	0	100.0	92.6
3	86	2	2.3	97.7	90.5
4	77	2	2.6	97.4	88.1
5	46	1	2.2	97.8	86.2

cent of the non-white; from 95 to 86 per cent showed stationary lesions throughout the period of observation.

The data presented in chart 1 also indicate that the risk of progression was highly concentrated within the first year after diagnosis of tuberculosis. Thirty-three per cent of the white and 49 per cent of the non-white patients with lesions of either exudative or exudative-productive type showed progression of disease within the first year; the proportions showing first signs of progression in subsequent years were relatively small; after the first year there was an average of about 6 per cent per year for both white and non-white patients. The non-white patients in the exudative and exudative-productive groups, as well as those with lesions of the productive and fibro-calcific types, showed a greater liability to progressive disease than did white patients in the corresponding groups.

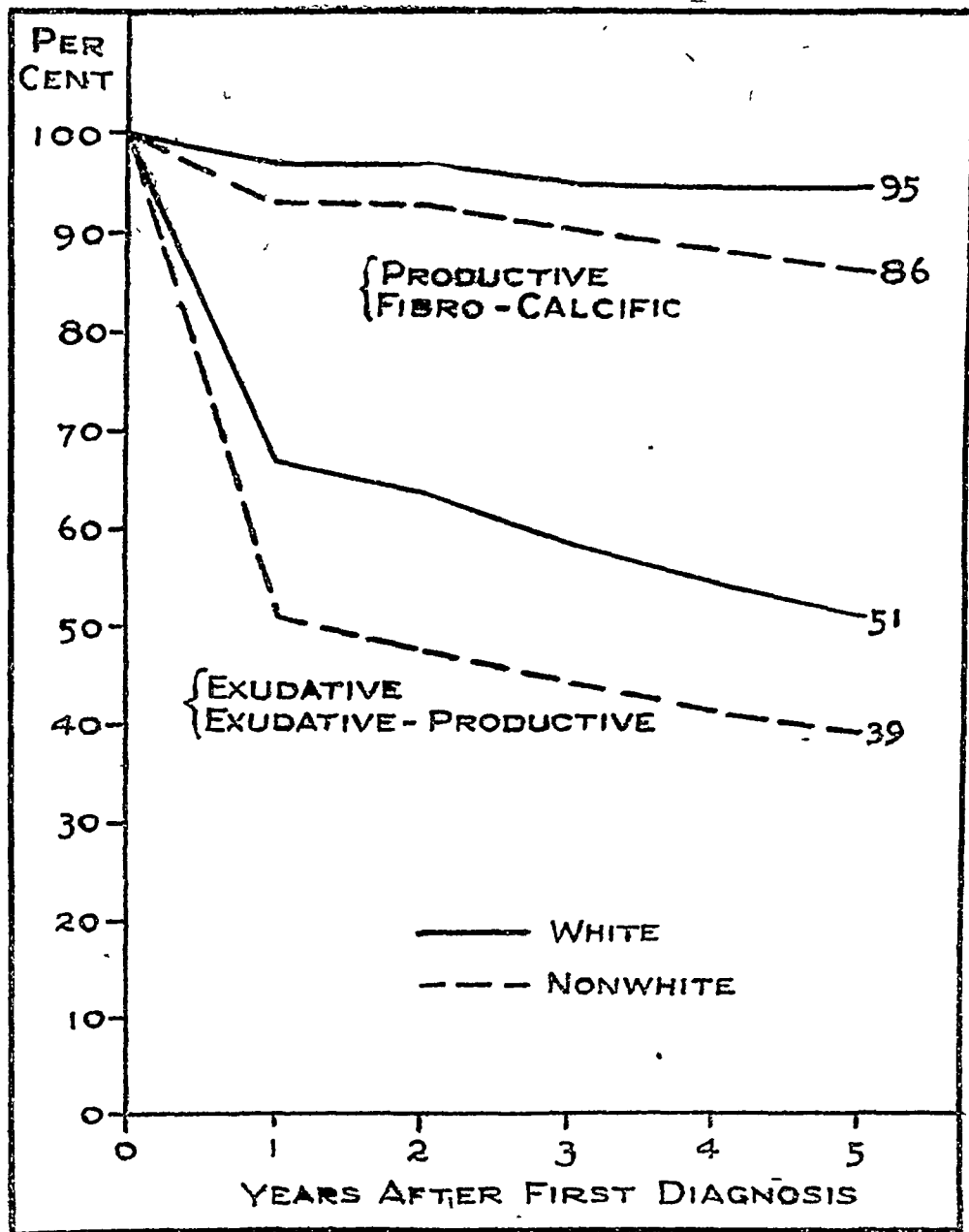


CHART 1. Percentage of cases of minimal tuberculosis showing no progression of disease during five years after initial diagnosis of tuberculosis

When the difference in the average rate of progressive disease for white and non-white patients is tested statistically for each type of lesion, the differences are of moderate significance or of borderline significance only, as shown in table 4.

The formula used for testing the significance of the difference is as follows:

$$\sigma \text{ diff.} = \sqrt{pq \left( \frac{1}{n_1} + \frac{1}{n_2} \right)}$$

In the formula  $p$  is the rate of progression,  $q$  is the rate of nonprogression in the combined sample of white and non-white cases;  $n_1$  is the total number of white patients with lesions of an exudative or exudative-productive character;  $n_2$  is the total number of non-white patients with lesions of exudative or exudative-productive character. Significance is indicated by the ratio of the difference to its standard error or  $\sigma$ . For a more complete explanation see Croxton and Cowden: Applied General Statistics, pp. 337-339.

There was no indication from the sample studied that five years was the limit of the period of risk of developing progressive disease for persons whose lesions were of the exudative or exudative-productive character. A larger sample with a more extended period of observation may be necessary before an approximate time limit of risk can be determined.

TABLE 4

CHARACTER OF LESION	AVERAGE RATE PER 100 PERSONS AND STANDARD ERROR OF RATE		DIFFERENCE AND STANDARD ERROR OF DIFFERENCE
	White	Non-white	
Exudative and exudative-productive.....	15.44 $\pm$ 1.79	22.83 $\pm$ 2.84	7.39 $\pm$ 3.22
Productive Productive-fibrotic } Fibrotic-calcific }	1.28 $\pm$ 0.45	3.06 $\pm$ 0.87	1.78 $\pm$ 0.90

In the group of cases with lesions classed as productive and fibrotic or fibro-calcific, all cases showing evidence of progression of disease during the five years after diagnosis had lesions of the productive or fibrotic type with the exception of one white patient whose lesion at the time of initial diagnosis was classified as fibro-calcific in character. This would indicate that there is a greater risk of progression for patients with lesions of the productive type than for those with fibro-calcific lesions.

The sample of cases studied is too small to measure precisely the risk of mortality of one lesion group as compared with another. However, the mortality of white and non-white persons can be compared. Table 5 shows the cases classified according to color of the patient and character of the lesion. It is apparent that non-white persons with exudative or exudative-productive lesions suffered a mortality considerably higher than did white persons in the same lesion group. When tested statistically this difference was found to be significant.<sup>3</sup> Both white and non-white persons with productive or fibro-calcific lesions suffered a relatively low mortality during the period studied. The difference between these rates was not found to be significant.<sup>4</sup>

<sup>3</sup> The difference between the rates, 2.5, was almost three times its standard error  $\pm 0.87$ .

<sup>4</sup> Since there was no indication from the sample studied that five years was the limit of the period of risk of developing progressive disease for persons whose lesions were of the exudative or exudative-productive character, it naturally follows that the risk of mortality from tuberculosis is not limited to a five-year period following initial diagnosis of minimal tuberculosis.



In interpreting the mortality data for the minimal cases studied it should be pointed out that there may be a more favorable mortality for the white patients with productive or fibro-calcific lesions than is generally true for persons with such tuberculous lesions. Thirty-one per cent of these cases came from a clinic population composed chiefly of civil service employees; that is, a group of a higher economic level than the remainder of the clinic population included in the study.

*Relationship of age to progressive disease:* The age of the patient is often regarded as a significant factor influencing the course and prognosis of tuberculosis. From a clinical standpoint, the potential seriousness of asymptomatic minimal lesions in adolescents and young adults has been particularly emphasized.

In the material of this study age proved to be a factor related to the risk of progressive disease chiefly in so far as it was associated with a particular character of the lesion. Lesions of the exudative and exudative-productive types were noted much more frequently at the younger ages (10 to 24 years) than were

TABLE 5

*Mortality among cases of minimal tuberculosis according to character of lesion and color of patient\**

CHARACTER OF LESION AND COLOR OF PATIENT	PERSON-YEARS AT RISK	NUMBER OF DEATHS	RATE PER 100 PERSON-YEARS
<i>Exudative and Exudative-Productive:</i>			
White persons.....	557	4	0.7
Non-white.....	348	11†	3.2
<i>Productive, Fibrotic, and Fibro-calcific:</i>			
White persons.....	644	1†	0.2
Non-white.....	423	2†	0.5

\* Period of observation from two to five years.

† One death from causes other than tuberculosis.

lesions of the productive-fibrotic and fibro-calcific types. For example, 44 per cent of the total white patients with exudative or exudative-productive lesions were under 25 years of age; only 11 per cent of those with productive-fibrotic or fibro-calcific lesions were in the same age group. Non-white patients showed a similar relationship between age of the individual and character of the lesion.

As shown in chart 1, exudative and exudative-productive lesions were found to be those most apt to result in progressive disease. Thus, if patients with lesions of this type are divided into two broad age groups, the proportions showing progressive disease are as follows:

Age Group	Per Cent Showing Progressive Disease
10-24 years.....	59
25 years and over.....	46

If, on the other hand, character of the lesion is not considered and the total sample is divided into the same two age groups, the results would appear to indicate a proportion with progressive disease almost three times greater in

persons 10 to 24 years of age than in those 25 years or over, as shown by the following figures:

Age Group	Per Cent Showing Progressive Disease
10-24 years.....	54
25 years and over.....	20

The importance of character of the lesion in relation to age may be summarized as follows: Eighty-five per cent of the total cases showing progression during five years after initial diagnosis had lesions of the exudative or exudative-productive type. Slightly less than 50 per cent of the progressive cases were patients under 25 years of age. The data from this study therefore indicate that if the factor of character of the lesion is considered, age *per se* becomes considerably less important, as far as the risk of developing progressive disease is concerned. The age factor does merit definite consideration from the point of view of prognosis to the extent that lesions of the exudative character, representing a presumably early and potentially progressive type of involvement, are more apt to be found in the younger age groups. It would seem, however, that comparable types of lesions occurring at any age represent a distinct risk of progressive disease.

*Behavior of the lesion during period of observation:* The potential and actual risk of persons with minimal tuberculous lesions may be presented also by classification of the behavior of the lesion during the period of observation. The cases were classified into four main types, as defined in a preceding paragraph, namely: frankly progressive, unstable, regressive and stationary.

Table 6 shows the behavior of the lesion during the five years' observation. Progressive lesions and unstable lesions, that is, those showing slight progression alternating with regression, were most frequent among patients with exudative lesions, 52 per cent of the white and 72 per cent of non-white persons falling into those categories. Patients with exudative-productive lesions showed less liability to progressive disease, but their risk was relatively great; approximately one-third of the group were classed as either frankly progressive or unstable. In only 5 per cent of white and 12 per cent of non-white patients with productive-fibrotic or fibro-calcific lesions was the behavior of the lesions described as either progressive or unstable, while 93 per cent and 87 per cent, respectively, exhibited a stable behavior throughout the period of observation.

Although the figures indicate a greater tendency among non-white than white patients to have progressive disease, because of the small number involved it cannot be stated with certainty whether the difference is real or due only to chance variations in sampling.

*Location of lesion:* In the majority of the cases with lesions of the exudative and exudative-productive character the roentgenogram showed either a purely subapical or combined apical and subapical lesion. In only a relatively small proportion of the patients presenting lesions of this type, 13 per cent, were the demonstrable changes limited to the apical region of the lung. On the other hand, among the cases with lesions classified as either productive-fibrotic or

fibro-calcific, the strictly apical location was far more frequent, 42 per cent, while in only 15 per cent were the lesions limited to the subapical area. There was, however, no indication from this study that the mere difference in location between lesions of comparable character was a significant factor related to the behavior of the lesion or subsequent course of the disease.

*Classification of stage and activity of the disease at the end of observation period:* The final diagnosis at the end of observation in cases of minimal tuberculosis is of interest because it shows strikingly the seriousness of progressive disease in relation to the character of the lesion on initial diagnosis. These data are shown

TABLE 6

*Behavior of the lesion in cases of minimal tuberculosis during period of observation*

CLASSIFICATION OF PROGRESS OF CASE	EXUDATIVE		EXUDATIVE-PRODUCTIVE		PRODUCTIVE AND FIBROTIC, OR FIBRO-CALCIFIC	
	White	Non-white	White	Non-white	White	Non-white
	<i>per cent</i>					
Total cases.....	100.0	100.0	100.0	100.0	100.0	100.0
Progressive.....	50.0	59.2	29.4	31.0	3.9	9.5
Unstable.....	2.3	13.0	5.9	6.9	1.3	3.2
Regression followed by stability.....	45.4	27.8	54.9	48.3	1.3	0
Stable throughout observation.....	2.3	0	9.8	13.8	93.5	87.3
	<i>number</i>					
Total cases.....	86	54	51	29	154	95
Progressive.....	43	32	15	9	6	9
Unstable.....	2	7	3	2	2	3
Regression followed by stability.....	39	15	28	14	2	0
Stable throughout observation.....	2	0	5	4	144	83

in table 7. From 50 to 62 per cent of the patients with exudative lesions were classed as either arrested or apparently cured tuberculosis; the remainder were considered as active and most of these had progressed either to the moderately advanced or far advanced stage of the disease. About one-fourth of the patients with exudative-productive lesions were classed as active, and in this group progression to advanced stages was also a prominent feature. Only a small proportion of the patients with productive-fibrotic or fibro-calcific lesions (3 to 5 per cent) had a final diagnosis of active disease at the end of the period of observation.

*Effect of treatment:* Approximately one-third of the total patients included in this study had some institutional treatment during the period of observation. Of the cases with lesions of exudative and exudative-productive character, 60 per cent had institutional care. Two-thirds of these had sanatorium treatment while in the minimal stage; the remaining one-third, or 20 per cent of the total patients

with exudative or exudative-productive lesions, received institutional treatment for the first time after the disease had progressed to an advanced stage. Only 14 per cent of the total cases showing lesions of a productive-fibrotic or fibro-calcific type had institutional treatment while the disease was in the minimal stage.

It would be highly desirable to evaluate the effect of treatment in minimal lesions upon the liability to progressive disease, the behavior of the lesion and the final status of the case at the end of the observation period. This would be of particular interest for patients showing minimal lesions of the exudative type which, as was shown here, present the greatest risk of progressive disease. Such

TABLE 7

*Distribution of cases of minimal tuberculosis according to diagnosis at the end of period of observation*

FINAL DIAGNOSIS	EXUDATIVE		EXUDATIVE-PRODUCTIVE		PRODUCTIVE AND FIBROTIC, OR FIBRO-CALCIFIC	
	White	Non-white	White	Non-white	White	Non-white
	<i>per cent</i>					
Total.....	100.0	100.0	100.0	100.0	100.0	100.0
Active						
Minimal.....	7.0	11.1	5.9	6.9	1.3	1.0
Moderately advanced.....	22.1	22.2	7.8	3.4	0.6	3.2
Far advanced.....	9.3	16.7	7.8	13.8	1.3	1.0
Arrested						
Minimal.....	31.4	16.7	31.5	17.3	5.9	9.5
Moderately advanced.....	3.5	3.7	3.9	3.4	0.6	0
Far advanced.....	0	0	0	0	0	0
Apparently cured						
Minimal.....	26.7	29.6	43.1	55.2	90.3	84.3
Number of cases.....	86	54	51	29	154	95

a study requires a high degree of comparability between the groups to be compared, that is, one with and the other without treatment. Because of a number of factors influencing the selection of cases for such groups, and also because of lack of uniformity as regards the type of treatment and length of institutional care, it was felt that the data obtainable from the present sample were not entirely suitable for analysis. It is hoped that data meeting all requirements for evaluation of the effect of treatment will be available in the future.

#### DISCUSSION

The data presented in this report indicate that within the category of "minimal tuberculosis" are included lesions of heterogeneous types and of different clinical significance. On the one hand there are lesions of a predominantly exudative

type, showing an unstable and often unpredictable behavior and in which the risk of progressive disease is great. Among these many undoubtedly represent a truly incipient manifestation of the disease, the subsequent evolution of which is extremely uncertain. At the opposite extreme there are the fibrotic and calcified lesions which represent a late form and, at the time of their first discovery, have already reached an advanced stage of healing. These are characterized by an essentially stable behavior and the indications are that they rarely lead to manifest clinical disease. Then there are intermediate forms representing gradations between the extreme types, both as to their morphologic characteristics and potential clinical significance.

The behavior of the lesion and the risk of progressive disease were found to be closely related to the character of the lesion at the time of initial diagnosis of the case. It must be admitted that a classification, such as employed in this study, which attempts to interpret roentgenological findings in terms of histopathological changes, has its distinct limitations and is subject to considerable inaccuracies. These may be due to the subjective factor of interpretation and in some measure also to variability in the technical quality of the roentgenogram.<sup>5</sup> It was thought, however, that from a practical standpoint this classification could serve as a suitable basis for qualitative differentiation of the types of lesions included in the minimal group.

There is reason to believe that the character of a given lesion is not the sole or even the most important factor influencing the future behavior of the disease in cases with minimal involvement. It is quite possible that the differences in volume and distribution of the pathological changes of the various types of lesions included within the accepted limits of the minimal stage may also be of considerable significance. It may be well to point out that from the standpoint of mere extent the lesions classified as falling within the minimal group are by no means uniform. They may range from involvement of a very small area just demonstrable on the roentgenogram to well pronounced changes comprising a sizable portion of the pulmonic field. To what degree such variations in extent and distribution among lesions of comparable character may affect the subsequent behavior and fate of the tuberculous process, would have to be determined by means of detailed special studies which would have to disregard the conventional classification according to stage of disease.

It must also be considered that there are probably a number of factors other than those related to the character or extent of the local disease focus that may affect the behavior of an existing lesion, even though their influence cannot be measured in precise terms. Racial differences, environmental conditions in the broadest sense, as well as variations in individual resistance, may all have a

<sup>5</sup> In a recent article dealing with comparative roentgenographic and pathological studies in experimental miliary tuberculosis in rabbits, Medlar, Pesquera and Ordway (*Am. Rev. Tuberc.*, 1944, 50, 1) emphasize the discrepancies between the changes observed in the roentgenogram and the pathological findings. It would be most interesting to carry out similar investigations in man, particularly on cases with localized lesions of chronic pulmonary tuberculosis of limited extent.

greater or lesser share in shaping the eventual outcome of the disease. In this respect patients with lesions of minimal extent are essentially not different from any other case of tuberculosis.

Although in this study emphasis was put on the significance of the roentgenological findings in minimal tuberculosis, it is obvious that for a complete appraisal of the lesion it is essential to consider all the clinical and laboratory data which may be helpful in the clinical evaluation of the case. It must be kept in mind, however, that little reliance can be placed on subjective symptoms since, as pointed out before, they are absent in the majority of cases. As regards the laboratory tests usually employed in tuberculosis, such as the erythrocyte sedimentation rate and the differential white cell picture, experience would indicate that they are only of limited practical value as the results are not consistent enough to be used as a reliable index of the state of activity or possible risk of a given lesion. Careful examination of the sputum and gastric contents, preferably by means of the culture or guinea pig method, is, of course, an essential requirement. At the same time it should be pointed out that in a considerable proportion of cases with minimal lesions of serious potentialities tubercle bacilli cannot be demonstrated despite a most diligent and exacting search.

It has often been stated that as a rule pulmonary tuberculosis if discovered in the minimal stage has a good prognosis. Many observers believe that a period of rest treatment is usually sufficient to result in arrest of the disease and to bring about lasting recovery in the majority of the cases. Wherett (5) and, more recently, Bobrowitz (6) reported that from 75 to 80 per cent of their patients in whom the disease was classified as "minimal" on admission to the institution were found to be apparently well after varying periods following their discharge. It is difficult to judge such data without adequate knowledge as to the distribution of the types of lesions included in the material studied. An appreciable proportion of cases with lesions of an essentially stationary character is bound to influence the results in a favorable direction. In a follow-up study of results of treatment in 185 cases of minimal tuberculosis, Kruger, Potter and Jaffin (7) found that about one-third of the cases with lesions classified as of the exudative type had shown progression, whereas among 75 cases in which the lesion was classified as productive, progression was observed in only one instance. The findings observed in the material of the present study do not lend support to some of the highly optimistic views regarding the behavior and ultimate prognosis of the exudative forms of minimal tuberculosis; that is, that type of lesion which may be considered as representing a presumably early manifestation of the disease.

It is precisely this type of lesion which presents an indication for therapeutic intervention. The lack of suitable data for analysis, and furthermore the fact that spontaneous regression is a frequent occurrence in lesions of this type, make an accurate appraisal of the effect of the usually employed method of rest treatment rather difficult. However, since in a large number of the cases, aside from the roentgenological findings, there are few reliable criteria for selection of the patients presenting risk of progressive disease, it is necessary to regard all those

exhibiting minimal lesions of a predominantly exudative character as of potential seriousness. It must also be emphasized that intensive supervision of the case over extended periods of time is of the utmost importance. For it would appear from the data presented in this report that the risk of progression may persist for a considerable length of time, even after regression with apparent stabilization of the lesion has occurred.

On the other hand, cases presenting minimal lesions of a chiefly productive and fibrotic or fibro-calcific type usually do not offer indications for therapeutic intervention. Inasmuch as the preponderant majority of such lesions tend to remain stationary, it would seem justified to permit those persons to carry on their normal mode of life, unless there are some clinical or laboratory findings suggestive of activity. It is also felt that there is need for selection of such cases for supervision on the basis of the potential risk of progression of the lesion.

#### SUMMARY AND CONCLUSIONS

1. The clinical significance of the tuberculous lesion of the lung of minimal extent was studied on the basis of a sample of 469 cases, the majority of which were observed for a period of five years or longer.

2. Under the term "minimal tuberculosis" are included lesions of diverse types, ranging from those of an apparently recent origin through those showing various gradations of healing, to lesions of an obviously old and obsolete type.

3. The majority of the patients showing involvement of minimal extent are asymptomatic and, aside from the roentgenological findings, present few objective criteria for evaluation of their clinical significance.

4. An appraisal of the clinical importance and presumable prognosis of the minimal tuberculous lesion requires a qualitative differentiation of the type of lesion. A classification based on the presumed pathological character of the lesion was employed in this study and the material was divided into four main categories, namely: exudative, exudative-productive, productive-fibrotic and fibro-calcific.

5. The character of the lesion at the time of initial diagnosis was found to be closely related to the behavior of the lesion and risk of progressive disease.

6. Lesions of the exudative or exudative-productive type are characterized by an unstable behavior and a distinct tendency to progression. Progression was observed in about one-half of the white patients and in 61 per cent of the non-whites. On the other hand, lesions classified as of productive-fibrotic or fibro-calcific character have shown a stationary behavior in the majority of instances, progression or instability having occurred in only 5 per cent of the white and in 14 per cent of the non-white patients. Lesions of the fibro-calcific type showed the highest rate of stability, progression being a rather exceptional occurrence in this type of involvement.

7. The minimal lesion of exudative character presents a definite hazard. Approximately one-half of the cases of this group presented evidence of active tuberculosis at the end of the observation period, the majority of them having

progressed to advanced stages of the disease. Only 3 to 5 per cent of the productive-fibrotic and fibro-calcific lesions had a diagnosis of active disease at the end of the period of observation.

8. For evaluation of the results of treatment in minimal tuberculosis it is of paramount importance to consider the character of the lesion at the time of initial diagnosis.

9. Supervision of the case of minimal tuberculosis should be on a selective basis and should take into account the risk of progressive disease as related to the character of the lesion.

#### SUMARIO Y CONCLUSIONES

1. Tomando por base una muestra de 469 casos, la mayoría de los cuales fueron observados por espacio de 5 años o más, se estudió el significado clínico de la lesión tuberculosa mínima del pulmón.

2. El término de "tuberculosis mínima" comprende lesiones de diversos tipos que varían de las de origen aparentemente reciente, pasando por las que revelan cicatrización de varios grados, a las lesiones de tipo manifiestamente antiguo.

3. La mayoría de los enfermos que revelan invasión mínima son asintomáticos y aparte de los hallazgos roentgenológicos, presentan pocos signos objetivos que permitan justipreciar la importancia clínica.

4. Una justipreciación de la importancia clínica y pronóstico presumible de la lesión tuberculosa mínima, exige una diferenciación cualitativa del tipo de la misma. En este estudio utilizóse una clasificación basada en la presunta naturaleza patológica de la lesión, dividiéndose el material en cuatro clases principales, a saber: exudativo, exudativo-productivo, productivo-fibrótico, y fibro-calcificado.

5. En el momento del diagnóstico inicial, la naturaleza de la lesión resultó estar íntimamente enlazada con el comportamiento de la lesión y el riesgo de enfermedad evolutiva.

6. Las lesiones del tipo exudativo o exudativo-húmedo caracterizanse por comportamiento inestable y tendencia decidida a la agravación. Esto se observó aproximadamente en la mitad de los enfermos blancos y en 61% de los otros. Por otro lado, las lesiones clasificadas como fibróticas-húmedas o fibro-calcificadas revelaron un comportamiento estacionario en la mayoría de los casos, habiéndose observado agravación o inestabilidad sólo en 5% de los enfermos blancos y 14% de los demás. Las lesiones del tipo fibro-calcificado revelaron el mayor coeficiente de estabilidad, constituyendo la agravación un hecho algo excepcional en esta clase de invasión.

7. La lesión mínima de naturaleza exudativa entraña un riesgo bien definido. Aproximadamente la mitad de los casos de este grupo presentaban signos de tuberculosis activa al terminar el período de observación, habiendo agravado la mayoría de ellos hasta llegar al período avanzado. Sólo en 3 a 5% de las lesiones húmedo-fibróticas o fibro-calcificadas se había hecho un diagnóstico de enfermedad activa al terminar el período de observación.



8. Para justipreciar el resultado del tratamiento en la tuberculosis mínima es de importancia primordial considerar la naturaleza de la lesión al hacer el diagnóstico inicial.

9. La vigilancia del caso de tuberculosis mínima debe realizarse sobre una base selectiva, tomando en consideración el riesgo de que se presente enfermedad evolutiva en relación con la naturaleza de la lesión.

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## TUBERCULOSIS MORTALITY IN COMMUNITIES OF DIFFERENT SIZE<sup>1</sup>

JACOB YERUSHALMY AND CHARLOTTE SILVERMAN

The living and working conditions and the very modes of life of people living in cities are different from those of rural residents. The 38 million persons who live in cities of 100,000 or more population are subject to different influences than are the 36 million living in the smaller cities or the 57 million scattered throughout the small villages and rural areas of the country.

The classification of people according to the size of community in which they live furnishes distinct groups which are differentiated by many socio-economic and occupational characteristics. The influences which these environmental factors have on the health and vitality of the population are sufficiently strong to be measurable in terms of the total mortality rate. In addition, many of the environmental conditions which are different for communities of different size exert a specific influence on tuberculosis mortality, which may be measured in terms of the death rate from tuberculosis.

Differences in the tuberculosis death rates reflect the collective effect of the many factors which differentiate communities of different sizes. However, for a better understanding of the epidemiology of tuberculosis it is also very useful to know whether the variations by size of community are similar for the two sexes, the various age groups and the different racial groups. A study of the similarities and differences in the behavior of the rate by sex, age and race makes possible a more satisfactory evaluation of the influence of certain of these factors on tuberculosis mortality. For example, as will be shown later, the variation in tuberculosis mortality by size of community is entirely different for females than for males. This finding is of assistance in interpretation, since it delineates the possible causal factors and limits consideration to only such conditions as are differently related to the sexes. In other words, factors such as housing, which affect both sexes in an essentially similar fashion, cannot be considered as major contributors to the differences in tuberculosis mortality among communities of different size. On the other hand, factors such as industrialization, which bear more strongly on adult males than on adult females, assume a more prominent rôle as a possible causal factor.

For the purpose of planning and developing tuberculosis control programs it is also necessary to analyze differences in mortality in considerable detail. For example, in mass X-ray survey work, it often becomes important to determine what combination of age-sex-race groups will yield the largest number of cases in different localities. This obviously, has a direct bearing on the practical consideration of the cost per case discovered.

The evaluation, on a national level, of differences in the mortality experience of residents of communities of different size was made possible by a recent publi-

<sup>1</sup> From the Tuberculosis Control Division, U. S. Public Health Service, Washington, D. C.

cation. Linder and Grove (1) of the Bureau of the Census published a very useful volume of natality and mortality rates for the country, which supplies the necessary data. The publication furnishes more detailed data on a "residence" basis than has heretofore been available for the analysis of mortality of residents of cities of different size and of rural areas. The data, to be sure, do not lend themselves to a very extensive analysis. For example, it is not possible to obtain complete tabulations by age, race, sex and population size for the different geographic divisions of the country. This paper, therefore, is limited to the analysis of tuberculosis mortality in its relation to mortality from all causes by size of community for the entire country.

There are a number of other limitations to the data which must be considered in evaluating and interpreting the results. The more important of these are:

1: In studying mortality from a specific cause, such as tuberculosis, it is important to bear in mind that the statistics may be influenced by the quality and quantity of medical care available to residents of communities of different size. Not all deaths from a given cause are diagnosed and reported as such on death certificates. It might be expected that a smaller proportion of correct diagnoses would be recorded in rural areas than in large cities where diagnostic facilities are more adequate. However, analysis by age, sex and race may assist in distinguishing differences that are real from those that result from misstatement of cause of death. If, for example, differences in rates are found among localities for one sex but not for the other, these variations could not be accounted for entirely by incomparability of diagnostic facilities.

2: The procedures for allocating deaths to place of residence are not entirely satisfactory in the case of tuberculosis. Because of the chronic nature of the disease it is difficult in some cases to allocate the death to the place of origin of the disease. For example, tuberculosis deaths which occur after more than one year of residence in a community and those occurring in mental and other institutions are assigned to the place of death which is not always the place of origin of the disease.

3: It should be borne in mind that classification by size of community presents the resident status of the population at a given specified period of time and is affected to a considerable extent by migration primarily from rural to urban areas. A certain proportion of the urban population consists of people who may have spent the major part of their lives in rural areas. This fact may be important in the evaluation of differences in mortality, since the migrating population may be a selected group from the point of view of health and vitality.

The literature on tuberculosis mortality and its association with environmental conditions is voluminous. A recent publication by Rich on *The Pathogenesis of Tuberculosis* (2) presents an exhaustive review of the literature as well as comprehensive discussions of many of the factors which have a bearing on this paper, particularly in the chapters on the influence of sex and age, factors that influence resistance and many others.

#### MORTALITY FROM ALL CAUSES BY SIZE OF COMMUNITY

Before proceeding with the study of tuberculosis mortality, it is desirable to determine how the total death rate (all causes) varies in cities of different size

TABLE 1

*Deaths (all causes) per 1,000 population by age, sex and race in cities of different size and in rural areas—United States, 1940*

AREA	DEATH RATES (ALL AGES)		AGE GROUPS								
	Crude	Standard- ized for age	Under 15	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85 and over
White—male											
United States (total).....	11.6	11.6	5.0	2.0	2.8	5.1	11.4	25.2	54.0	122.2	249.3
Places having a popula- tion of:											
100,000 and over.....	12.2	12.5	4.5	1.6	2.6	5.6	13.5	30.3	62.4	129.0	215.2
2,500-100,000.....	12.7	12.6	5.9	2.1	3.0	5.4	12.3	27.7	59.3	129.5	267.3
10,000-100,000.....	12.2	12.4	5.4	2.0	2.8	5.2	12.1	27.6	59.3	128.5	256.4
2,500- 10,000.....	13.6	13.2	6.8	2.5	3.4	5.9	12.6	27.9	59.4	131.5	286.6
Rural areas.....	10.6	10.3	4.8	2.1	2.8	4.4	9.0	20.0	46.2	114.6	255.1
Urban areas (2,500 popu- lation and over).....	12.4	12.6	5.2	1.9	2.8	5.5	12.9	29.1	60.8	129.3	243.7
Places of 10,000 and over.	12.2	12.5	4.9	1.8	2.7	5.4	13.0	29.3	61.1	128.8	233.1
Places under 10,000.....	11.1	10.8	5.1	2.1	2.9	4.7	9.7	21.4	48.4	117.5	260.5
White—female											
United States.....	9.2	8.8	3.8	1.4	2.2	3.7	7.5	16.8	41.5	105.6	224.7
Places having a popula- tion of:											
100,000 and over.....	9.6	9.2	3.4	1.2	2.1	3.8	8.3	19.2	45.7	109.7	208.0
2,500-100,000.....	10.0	9.1	4.5	1.5	2.3	3.8	7.8	17.4	42.1	106.0	232.1
10,000-100,000.....	9.8	9.0	4.2	1.4	2.2	3.7	7.8	17.6	42.3	106.2	227.1
2,500- 10,000.....	10.4	9.4	5.1	1.7	2.5	4.0	7.8	17.1	41.6	105.6	241.8
Rural areas.....	8.3	8.2	3.7	1.4	2.2	3.4	6.4	14.4	37.8	102.4	230.0
Urban areas (2,500 popu- lation and over).....	9.8	9.2	4.0	1.4	2.2	3.8	8.1	18.3	43.9	107.7	221.0
Places of 10,000 and over.	9.7	9.1	3.7	1.3	2.1	3.8	8.1	18.6	44.3	108.2	216.4
Places under 10,000.....	8.7	8.4	3.9	1.5	2.3	3.5	6.6	15.0	38.6	103.1	234.8
Nonwhite—male											
United States.....	15.1	17.5	8.5	5.0	8.5	13.2	24.5	39.5	56.5	109.7	193.2
Places having a popula- tion of:											
100,000 and over.....	16.5	19.1	8.3	5.6	9.1	14.1	27.3	44.8	68.4	118.7	143.2
2,500-100,000.....	18.8	21.3	10.7	6.6	10.6	15.9	29.8	51.2	65.7	122.8	207.7
10,000-100,000.....	18.1	20.8	10.1	6.3	10.4	15.5	29.3	50.5	65.7	118.5	193.9
2,500- 10,000.....	20.4	22.5	12.1	7.3	11.1	17.1	31.0	52.7	65.5	130.0	230.4

TABLE 1—*Continued*

AREA	DEATH RATES (ALL AGES)		AGE GROUPS								
	Crude	Stand- ard- ized for age	Under 15	15-24	25-34	35-44	45-54	55-64	65-74	65-84	85 and over
Nonwhite—male— <i>Continued</i>											
Rural areas.....	13.1	15.1	7.9	4.2	7.2	10.9	20.0	32.1	49.3	102.8	201.9
Urban areas (2,500 popu- lation and over).....	17.5	20.1	9.4	6.1	9.7	14.8	28.3	47.5	67.0	120.9	177.7
Places of 10,000 and over.	17.1	19.7	9.0	5.9	9.5	14.5	28.0	46.7	67.4	118.6	164.4
Places under 10,000.....	13.9	15.9	8.3	4.5	7.7	11.7	21.3	34.4	51.0	105.8	204.9
Nonwhite—female											
United States.....	12.6	14.9	6.8	5.0	7.4	11.7	21.1	35.7	46.3	84.7	156.2
Places having a popula- tion of:											
100,000 and over.....	13.1	15.6	6.6	5.4	7.0	11.7	22.6	37.9	52.8	89.9	125.0
2,500-100,000.....	14.8	17.0	8.2	5.9	8.4	13.5	24.6	43.1	49.2	85.3	160.2
10,000-100,000.....	14.5	16.9	7.9	5.8	8.1	13.2	24.7	43.2	49.1	86.2	151.5
2,500- 10,000.....	15.6	17.4	9.0	6.1	9.0	14.1	24.3	42.8	49.2	83.8	174.9
Rural areas.....	11.3	13.6	6.4	4.5	7.1	10.7	18.1	30.9	41.7	82.2	165.4
Urban areas (2,500 popu- lation and over).....	13.9	16.2	7.3	5.6	7.6	12.4	23.4	40.1	51.0	87.6	143.6
Places of 10,000 and over.	13.6	16.0	7.0	5.6	7.4	12.2	23.3	39.7	51.4	88.4	136.0
Places under 10,000.....	11.8	14.1	6.6	4.7	7.4	11.2	19.0	32.5	42.8	82.4	166.5

and in rural areas. This will permit comparison between the two rates and indicate how the differences in tuberculosis mortality by size of community fit into the framework of the variations in total mortality.

Table 1 presents the death rates (all causes) by age, race and sex for 1940 in cities of different size and in rural areas. The analysis of the data in table 1 as well as that for tuberculosis mortality will be presented in three main groups of community size: the large cities (100,000 or more population), intermediate-sized cities (2,500 to 100,000<sup>2</sup>) and rural areas (less than 2,500). In terms of the total population included in these groups the large cities contain 37,987,969

<sup>2</sup> The small cities (2,500 to 10,000) were combined with cities of 10,000 to 100,000 because the rates for these cities may not be as accurate as those for the larger cities. From table 1 it appears that the mortality rates in the small cities are the least favorable. This may be a true fact but it is possible that it may be the result of errors introduced in the process of allocating deaths to place of residence. Errors regarding the legal limits of cities and towns may be relatively large for small cities. See *l.c.* page 14.

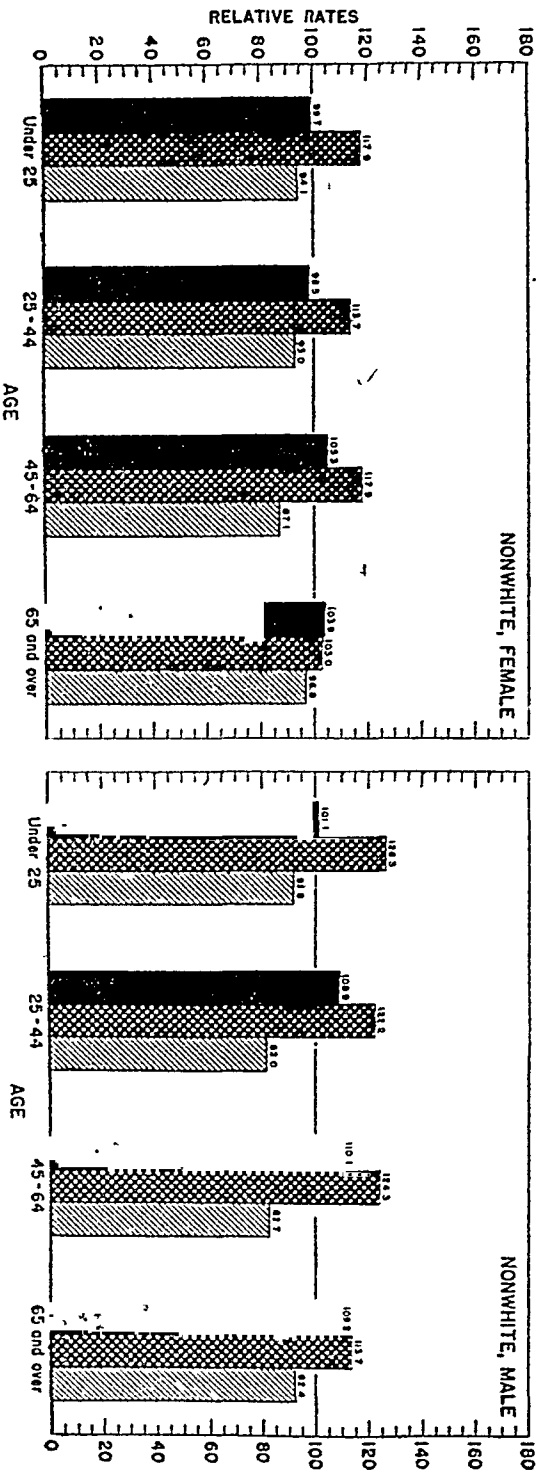
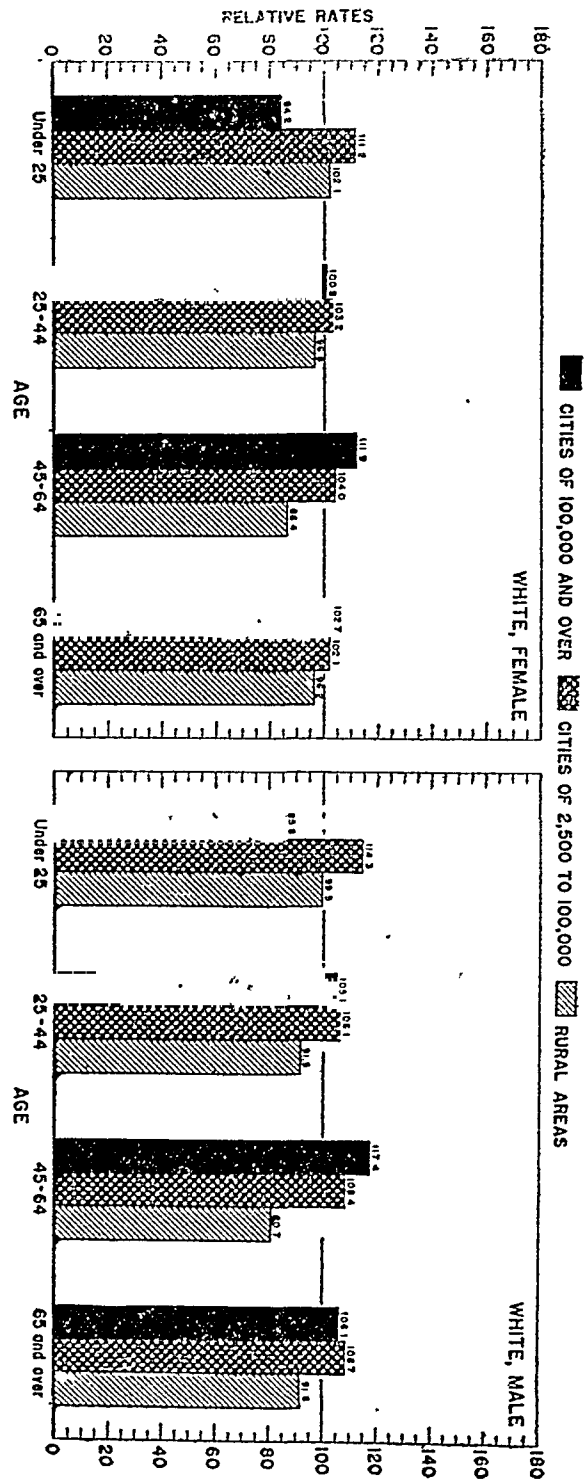


CHART 1. Relative mortality from all causes in communities of different size by age, race and sex—United States, 1940.  
(Rates in each population size group shown as a percentage of the total rate for the corresponding age-race-sex group.)

people (29 per cent of the total population), the intermediate-sized cities, 36,435,-713 (28 per cent), and the rural areas contained 57,245,573 people (43 per cent). The data in table 1 are illustrated in chart 1 for four broad age groups which may be thought of in terms of occupational periods as follows: pre-occupational, maximum activity, moderate activity and old age.<sup>3</sup> In order to facilitate comparisons between the various age groups with different levels of mortality, *relative* rather than *actual* rates are presented. In other words, the death rate in each community size is shown as a percentage of the death rate for the country as a whole for each race-sex-age group.

It may be seen from table 1 that the crude death rates (all ages combined) are higher in the cities than in the rural areas for all four race-sex groups. However, the variations in mortality by size of community are not similar in the four broad age groups. Most striking is the fact that in the pre-occupational period the rates, particularly among whites, are lower in large cities than in rural areas. The favorable rates of the rural population become evident only after age 35. This may be explained by the assumption that in the younger ages the city dwellers have the advantages of better medical and sanitary facilities and that these advantages are offset in adult life by occupational and health hazards to which the urban population may be exposed during periods of gainful employment. In this connection it is interesting to observe that, whereas in the pre-occupational ages the relative rates are nearly the same for each sex, among adults the increase in rates in urban areas, as compared with rural areas, is greater for males than for females.

The higher rates in urban than in rural communities are observed most prominently in the age group 45 to 64 rather than in the ages of maximum activity. This may indicate the cumulative effect of industrial hazards. In the case of females another factor which may be operating to depress the relative rates in urban areas during the most productive age period is that of higher fertility rates of rural than urban women. Rural women during the child bearing ages may be exposed more frequently to morbidity and mortality associated with reproduction than are urban women.

It is also of interest to note that among nonwhites in almost all age groups the rates were highest in intermediate-sized cities, followed by those in large cities and lowest in rural areas, while among whites the rates were generally highest in the large cities.

#### MORTALITY FROM TUBERCULOSIS (ALL FORMS) BY SIZE OF COMMUNITY

In some respects the variations in tuberculosis mortality by size of community are similar to those of the total death rate. There are, however, a number of significant and interesting differences in the behavior of the two rates. Foremost is the fact that, in tuberculosis, the rate for females varies with size of city entirely differently than does the rate for males. While the latter is generally

<sup>3</sup> Because the rates in the original publication are given in 10 and 15 year age groups, the best age classifications that could be obtained are: under 25, 25 to 44, 45 to 64, and 65 and over.

TABLE 2

*Deaths from tuberculosis (all forms) per 100,000 population by age, sex and race in cities of different size and in rural areas—United States, 1940*

AREA	DEATH RATES (ALL AGES)		AGE GROUPS									
	Crude	Stand- ard- ized for age	Under 15	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85 and over	
White—male												
United States (total)	44.7	44.0	5.4	17.0	40.2	59.2	83.6	103.0	102.3	90.9	67.4	
Places having a popula- tion of:												
100,000 and over.....	55.5	51.6	7.2	17.9	42.8	67.2	99.3	130.4	125.7	101.7	78.7	
2,500-100,000.....	44.2	42.8	6.0	16.7	39.6	58.5	82.1	98.2	97.2	78.2	40.2	
10,000-100,000.....	42.0	40.4	5.2	15.1	38.5	53.5	77.8	93.8	95.5	67.8	55.1	
2,500- 10,000.....	48.8	48.0	7.6	20.1	41.9	69.4	91.8	107.8	100.5	96.5	13.9	
Rural areas.....	38.1	39.4	4.2	16.7	38.6	53.0	71.5	87.0	92.2	93.1	77.4	
Urban areas (2,500 popu- lation and over).....	49.9	47.3	6.6	17.3	41.2	63.1	91.3	114.9	111.1	88.9	57.7	
Places of 10,000 and over.	50.2	47.2	6.4	16.8	41.1	62.0	91.2	116.2	113.4	87.0	68.5	
Places under 10,000.....	39.9	40.9	4.7	17.2	39.2	56.1	75.2	90.5	93.6	93.7	66.6	
White—female												
United States.....	28.3	27.8	5.6	27.7	39.8	33.3	28.7	36.4	55.1	69.7	54.9	
Places having a popula- tion of:												
100,000 and over.....	26.7	25.2	7.0	27.8	36.5	30.4	24.9	29.7	41.1	50.1	35.5	
2,500-100,000.....	28.2	27.1	6.6	26.9	39.2	32.1	27.7	33.5	51.8	63.8	50.9	
10,000-100,000.....	26.1	25.0	6.6	25.2	36.4	28.4	25.4	30.1	48.1	58.4	48.1	
2,500- 10,000.....	32.7	31.6	6.5	30.4	45.2	40.6	32.9	40.8	59.5	74.4	56.3	
Rural areas.....	29.5	30.9	4.5	28.1	43.4	37.0	32.9	44.2	68.8	88.9	71.1	
Urban areas (2,500 popu- lation and over).....	27.4	26.1	6.8	27.3	37.8	31.2	26.2	31.6	46.5	57.5	43.8	
Places of 10,000 and over.	26.5	25.1	6.9	26.8	36.4	29.6	25.1	29.9	44.0	53.7	41.0	
Places under 10,000.....	30.1	31.0	4.8	28.5	43.8	37.7	32.9	43.5	66.8	85.7	68.7	
Nonwhite—male												
United States.....	139.1	148.1	27.4	141.8	201.2	215.2	227.7	201.2	152.7	133.3	90.1	
Places having a popula- tion of:												
100,000 and over.....	217.7	210.9	46.7	215.1	266.7	283.9	313.8	331.7	223.3	157.0	76.4	
2,500-100,000.....	157.7	158.7	38.2	169.3	201.0	221.3	248.2	191.0	157.1	152.4	66.4	
10,000-100,000.....	161.6	162.2	39.6	168.7	206.5	223.4	246.9	205.8	159.1	206.1	53.3	
2,500- 10,000.....	149.2	151.6	35.4	170.6	188.4	216.0	251.1	158.9	153.5	63.8	88.0	



TABLE 2—*Continued*

AREA	DEATH RATES (ALL AGES)		AGE GROUPS								
	Crude	Stand- ard- ized for age	Under 15	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85 and over
<i>Nonwhite—male—Continued</i>											
Rural areas.....	93.7	107.8	18.0	104.9	158.5	150.9	154.4	135.2	126.6	120.4	101.0
Urban areas (2,500 popu- lation and over)....	191.8	188.8	42.8	193.6	238.8	260.3	288.1	272.9	190.7	154.6	71.0
Places of 10,000 and over.	198.5	194.5	44.1	197.6	246.3	265.6	293.0	290.2	198.6	177.5	66.7
Places under 10,000.....	99.4	112.7	19.4	111.3	162.3	159.6	167.2	135.4	129.5	114.0	99.6
<i>Nonwhite—female</i>											
United States.....	117.2	117.0	31.3	189.1	191.9	134.7	107.7	100.3	64.0	50.4	72.0
Places having a popula- tion of:											
100,000 and over.....	153.9	144.9	63.0	279.7	202.9	146.1	116.8	97.4	56.9	33.4	48.5
2,500-100,000.....	125.0	117.2	26.8	192.7	202.5	130.7	111.0	97.3	50.8	65.7	—
10,000-100,000.....	125.7	117.1	27.4	201.5	198.9	123.3	116.3	90.0	47.3	61.3	—
2,500- 10,000.....	123.4	117.7	25.6	173.7	211.1	149.2	98.9	112.9	57.5	73.5	—
Rural areas.....	93.7	102.8	21.9	144.7	176.5	126.6	99.2	103.5	73.7	51.1	107.4
Urban areas (2,500 popu- lation and over)....	141.2	132.1	46.3	238.5	202.7	139.9	114.4	97.4	54.0	49.6	22.9
Places of 10,000 and over.	144.0	134.7	50.0	249.9	201.5	138.8	116.7	94.8	53.3	44.4	28.4
Places under 10,000.....	97.2	105.1	22.2	149.8	181.7	129.9	99.2	104.8	71.4	54.1	94.1

higher in the urban areas, the rate for females decreases with increasing size of community—the highest rate being recorded for rural areas.

Table 2 presents tuberculosis mortality rates by the same classification used in table 1 for the total death rate. The data in table 2 are illustrated in chart 2 which presents age-specific mortality rates by race and sex in three population-size groups, and in chart 3 which shows the same information in broad age groups on a relative basis to facilitate comparison with the total death rate as given in chart 1. The analysis is presented separately for each race-sex group, since in tuberculosis, even more than in the total death rate, the combined rate for the two sexes and races is misleading because it is the resultant of components operating in different directions.

*White male:* The crude death rate from tuberculosis (all forms) among white males was found to be highest in the large cities (55.5 per 100,000 population), followed by the intermediate-sized cities (44.2), with the lowest rate recorded in the rural areas (38.1). The combined rate for all cities (49.9) was higher than that for the rural areas by 31 per cent.

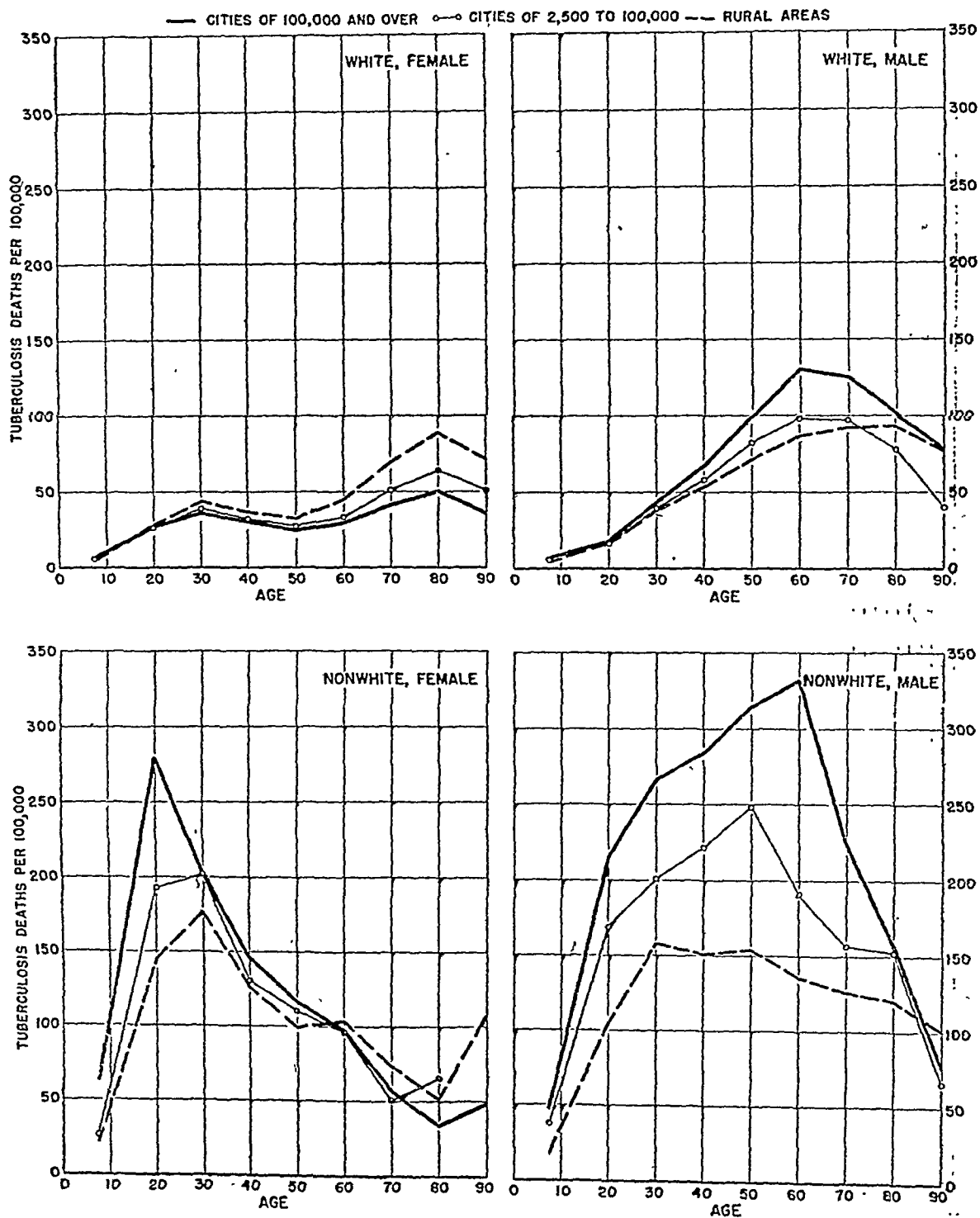


CHART 2. Tuberculosis mortality by age, race and sex in communities of different size—United States, 1940.

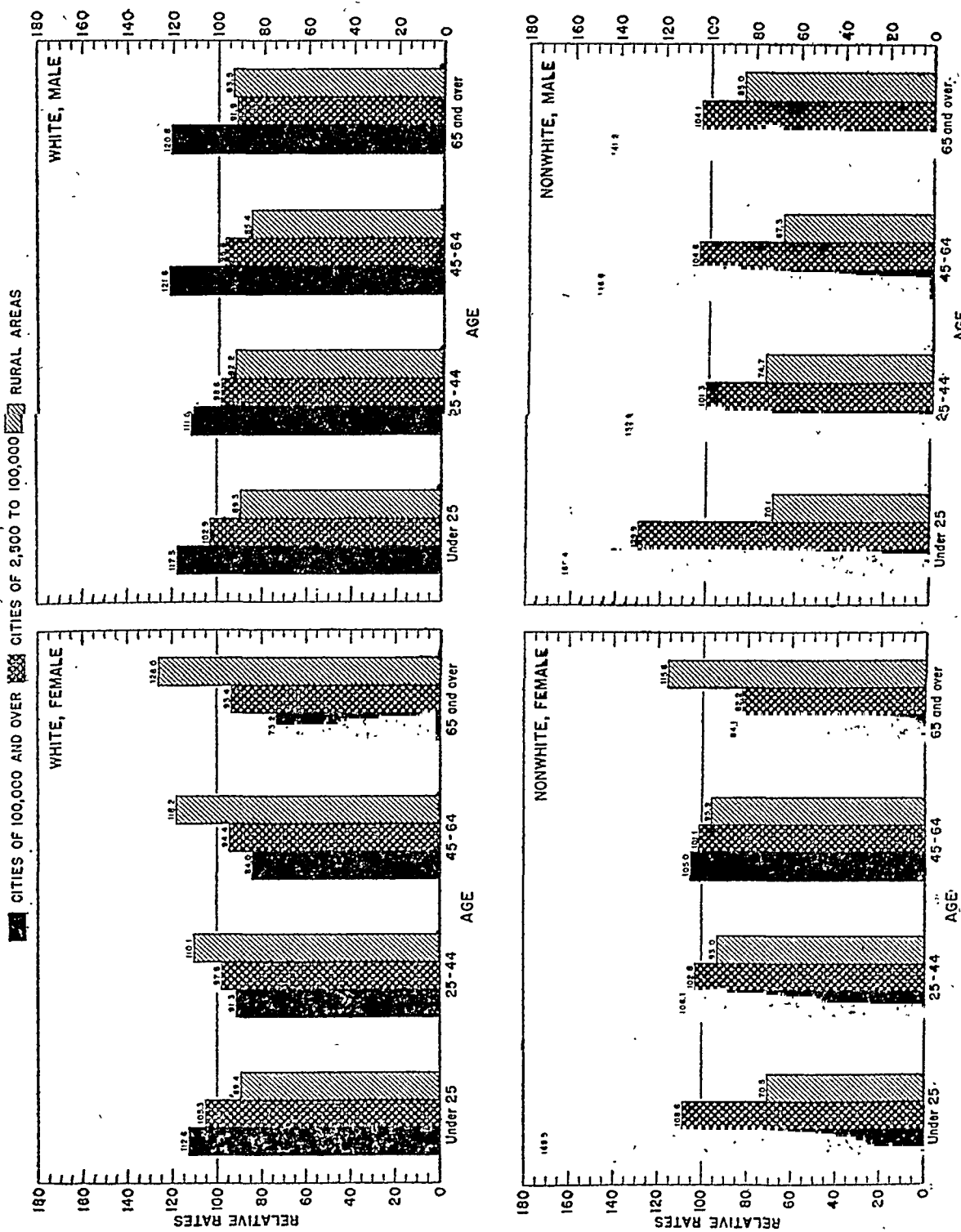


CHART 3. Relative mortality from tuberculosis in communities of different size by age, race and sex—United States, 1910.  
(Rates in each population size group shown as a percentage of the total rate for the corresponding age-race-sex group.)

The rate increased with size of city in practically every one of the age groups, but was more pronounced in the older than in the younger ages. An outstanding difference between mortality from tuberculosis and the total death rate for this race-sex group is the fact that in tuberculosis the higher rates in the large cities also prevailed during the pre-occupational age period, while the total death rate for the pre-occupational age group was more favorable in the cities.

*White female:* The variations in tuberculosis mortality by size of community were found to be different for females than for males. The crude death rate from tuberculosis (all forms) for white females was highest in the rural areas (29.5), followed by intermediate-sized cities (28.2), and lowest in large cities (26.7).

In the youngest age group, the situation was very much like that found for males, with the highest rate recorded for the large cities and the lowest rate in the rural areas. After puberty, however, a reversal appeared. The rate in the large cities was lower than that in the intermediate-sized cities, which, in turn, was exceeded by the rural rate. The rate in the rural areas remained above the other two for the entire life span and the excess increased with age.

*Nonwhite male:* The correlation between tuberculosis mortality and size of community is prominently observed among nonwhite males. The crude rate for the large cities (217.7) was higher by 38 per cent than that for intermediate-sized cities (157.7), which in turn exceeded by 68 per cent the crude rate for rural areas (93.7). The rate for the latter was less than half that for all urban areas. A similar correlation for each one of the age groups can be seen in charts 2 and 3.

*Nonwhite female:* The situation among nonwhite females was different from that of any other race-sex group. The variation of the rate with size of city is not uniform in the different age groups. Up to age 35 the relative standing of the rate in the three types of communities was similar to that found among males. Beginning with age 35, however, the difference in the rate between the large cities and the rural areas diminished and no significant difference was found between the urban and rural rates.

#### DISCUSSION

Two main points emerge from the foregoing data on tuberculosis mortality:

1. *The variation of the rate with size of community is different for adult males than for adult females.* Among adult males of the two race groups, tuberculosis mortality *increases* with increasing size of community; among adult white females, the rate *decreases*, and for nonwhite adult females the rate is practically the same in all population size communities.

This difference between the sexes may be brought out more clearly by bringing together on the same chart the rates for males and for females in communities of different size (see charts 5 and 6). It becomes strikingly evident that in large cities the rate differences between the sexes are great; the curve for adult males lying far above that for adult females. In rural areas there is only a slight difference in tuberculosis mortality between the sexes.

2. *There is no difference in the variation of the rates by sex with size of community during childhood and adolescence.* In each of the four race-sex groups tuberculosis in this age period is highest in the large cities and lowest in the rural areas.

It is significant that in these two respects tuberculosis mortality behaved differently from total mortality (all causes). It will be recalled that the death rate from all causes among females is not higher in rural than in urban areas, and in childhood and adolescence mortality from all causes is more favorable in the large cities.

Since it is desirable to distinguish differences which are specific for tuberculosis from those of total mortality, it may be well to determine in more detail the extent to which the variations in tuberculosis mortality by size of community differ from those of the total death rate. This may be accomplished by what is generally known as "proportionate mortality," which presents the number of deaths from tuberculosis out of every 100 deaths from all causes. The changes in "proportionate mortality" for communities of different size indicate the magnitude of the variations in tuberculosis mortality over and above those which may be expected from differences in the total death rate. For example, if tuberculosis mortality varies with size of community essentially in the same way and to the same degree as does the total death rate, there would be no significant differences in proportionate mortality and the curves for the different sized communities would be nearly superimposed on one another. However, if the curve for one community lies above that of another it signifies that the increase in tuberculosis mortality for that community is greater than that of the total death rate.

A review of table 3 and chart 4 shows that for white males the increase in tuberculosis mortality in the large cities is greater than that of the total death rate up to age 40. After that age tuberculosis varies much like mortality from all causes. For white females under 25 years of age the increase in the large cities is higher for tuberculosis than for total mortality, but after age 25 the situation is reversed and the unfavorable tuberculosis rates in rural areas are apparent. For nonwhite males of all ages and for nonwhite females under 40 the magnitude of the tuberculosis problem in the large cities over and above that of total mortality is striking. The variation of the death rate from tuberculosis with size of community among nonwhite females over 40 is similar to that of total mortality.

Admittedly, the material at hand is not sufficient to explain the factors which may be responsible for the differences in tuberculosis mortality. The difficulty of isolating causal factors is apparent when it is realized that medical care, housing, sanitation, nutrition, exposure, industrialization are only some of the environmental conditions which may be of significance. Nevertheless, it may be permissible to speculate on the mode of operation of certain of these conditions which may be more intimately associated with tuberculosis.

The selection of these factors for discussion need not be determined arbitrarily but may be guided by the analysis presented above. It is apparent that the sex and age difference in the behavior of the rate brings certain factors into sharper focus. For example, some of the conditions which are different for

residents of communities of different size such as housing, sanitary conditions, medical care and possibly nutrition are probably related to the two sexes in an essentially similar fashion and consequently could not be considered as contributing substantially to the observed sex differences. On the other hand, factors such as exposure, industrialization and, of course, fertility affect the two sexes dif-

TABLE 3

*Deaths from tuberculosis (all forms) as percentages of deaths from all causes in cities of different size and in rural areas—United States, 1940*

AREA	AGE GROUPS									
	All ages	Under 15	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85 and over
White—male										
Places having a population of:										
100,000 and over....	4.5	1.6	10.9	16.2	12.0	7.4	4.3	2.0	0.8	0.4
2,500-100,000.....	3.5	1.0	7.8	13.2	10.9	6.7	3.5	1.6	0.6	0.2
Rural areas.....	3.6	0.9	8.1	13.8	12.1	7.9	4.3	2.0	0.8	0.3
White—female										
Places having a population of:										
100,000 and over....	2.8	2.1	22.7	17.7	7.9	3.0	1.5	0.9	0.5	0.2
2,500-100,000.....	2.8	1.5	18.0	17.3	8.5	3.5	1.9	1.2	0.6	0.2
Rural areas.....	3.5	1.2	19.4	19.6	10.8	5.1	3.0	1.8	0.9	0.3
Nonwhite—male										
Places having a population of:										
100,000 and over....	13.2	5.6	38.4	29.3	20.2	11.5	7.4	3.3	1.3	0.5
2,500-100,000.....	8.4	3.6	25.5	19.0	13.9	8.3	3.7	2.4	1.2	0.3
Rural areas.....	7.2	2.3	24.9	22.2	13.9	7.7	4.2	2.6	1.2	0.5
Nonwhite—female										
Places having a population of:										
100,000 and over....	11.7	9.6	51.7	29.1	12.4	5.2	2.6	1.1	0.4	0.4
2,500-100,000.....	8.4	3.2	32.8	24.1	9.7	4.5	2.3	1.0	0.8	—
Rural areas.....	8.3	3.4	32.2	24.7	11.8	5.5	3.3	1.8	0.6	0.6

ferently. In a similar way, the various age groups are not influenced to the same extent or in the same manner by all of these conditions. In addition, many of the factors which are not specific for tuberculosis but which may have a contributory effect in lowering individual resistance, also affect the total death rate. In attempting to explain the variations observed in proportionate mortality it is, therefore, necessary to look for more specific factors than those

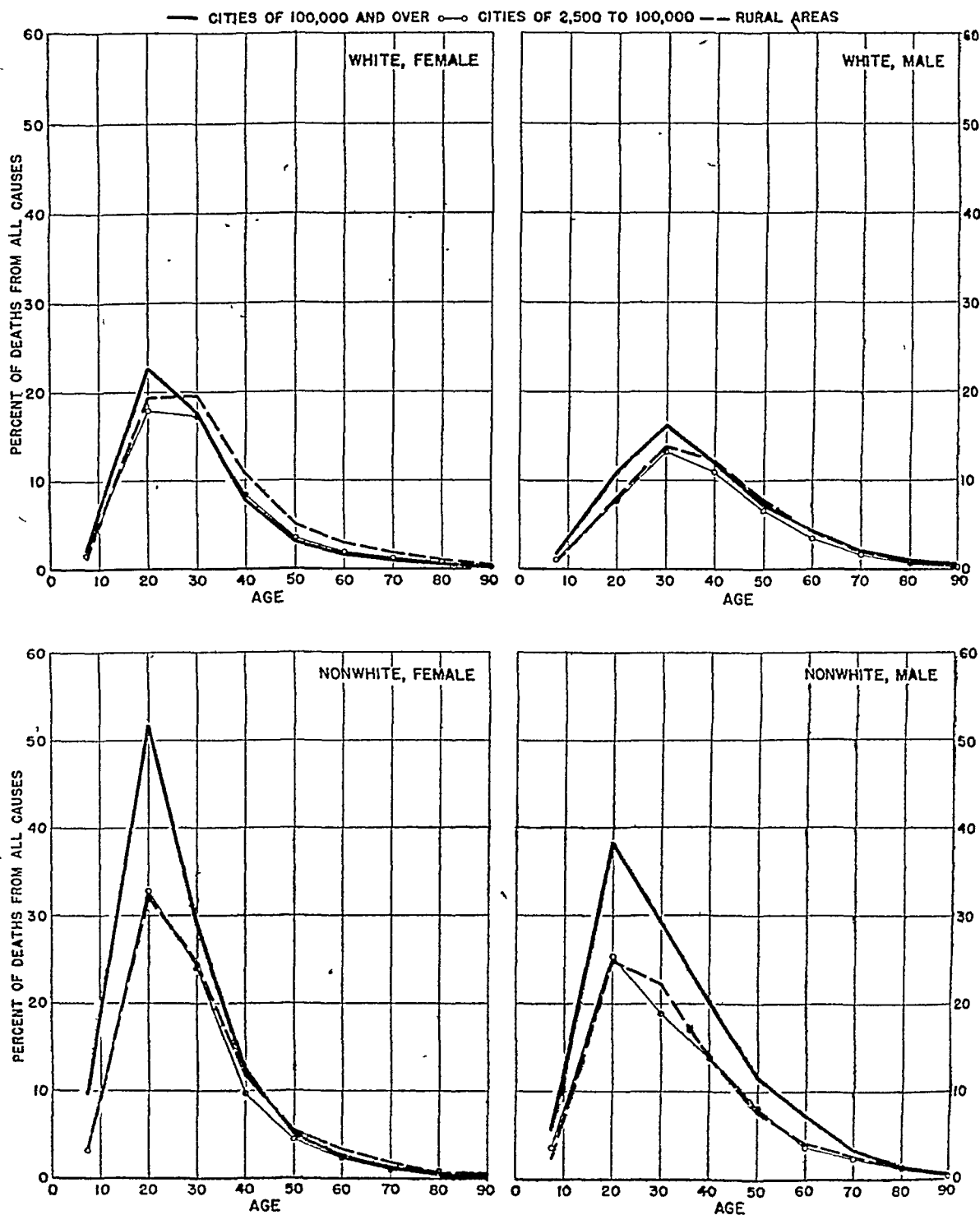


CHART 4. Deaths from tuberculosis as percentage of deaths from all causes by age, race and sex in communities of different size—United States, 1940.

affecting in a general way the "standard of living" of residents of communities of different size.

In light of the observed age and sex differences in tuberculosis mortality and in proportionate mortality the group of factors to be studied is narrowed considerably. For the purposes of this paper it was thought that three factors might be selected for discussion since they appear to be more specifically related to tuberculosis mortality and their effect is different for the two sexes and the various age groups. These are:

- 1: Opportunities for exposure to the disease.
- 2: Fatigue, exhaustion or strain and lack of sufficient rest.
- 3: Fertility.

The source of the spread of tuberculosis in a community is the sum total of all open cases of the disease in the locality. Consequently the greater the opportunities for exposure to open cases the higher the prevalence of tuberculosis morbidity and mortality in a community. The greater prevalence of tuberculosis in the more densely populated areas is reflected in the higher rates for children in these localities. The fact that little or no sex difference is observed in the relative rates for the younger age groups may be explained by the assumption that tuberculosis in these ages is acquired primarily through familial contact and therefore both sexes are equally exposed.

Among adults, the exposure factor is somewhat different, since the main source of contact may be extrafamilial. The higher rates among males in urban areas may be explained, at least in part, by assuming that in the cities they are more often in contact with larger population groups than are males in more sparsely populated communities.

The factor of extrafamilial contact may not be so pronounced for females. In general the city housewife is not exposed to much greater continuous close contact with large groups of the population than her rural sister. On the other hand, one may expect slightly higher rates in the cities among females on the basis of the higher rates among their consorts. The fact that the rates for white females are actually lower in cities than in rural areas indicates that factors other than contact must be operating.

In attempting to account for this latter fact it may be necessary to make certain hypotheses about the modes of life and working conditions of white females in urban and rural areas. It is possible that hard work with resulting fatigue may play a rôle. If it is true that rural housewives in general work longer and harder, perform many chores on the farm and in the yard and do not have available to them as many labor saving devices as the city women have, then the associated fatigue and lowered resistance may contribute towards higher tuberculosis mortality rates among rural than urban women.

It should be noted that no significant difference by size of community was observed among nonwhite women. This may be explained if it is assumed that the advantages of urban living conditions are not available to them to the same degree as to the white residents.



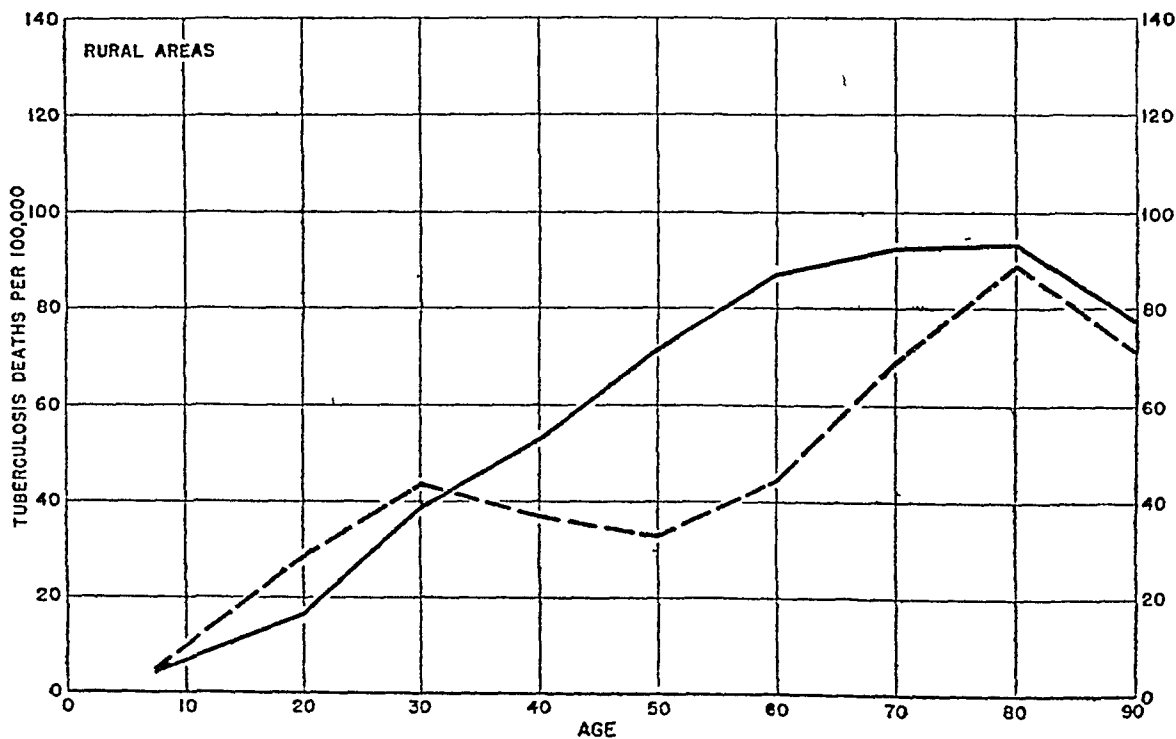
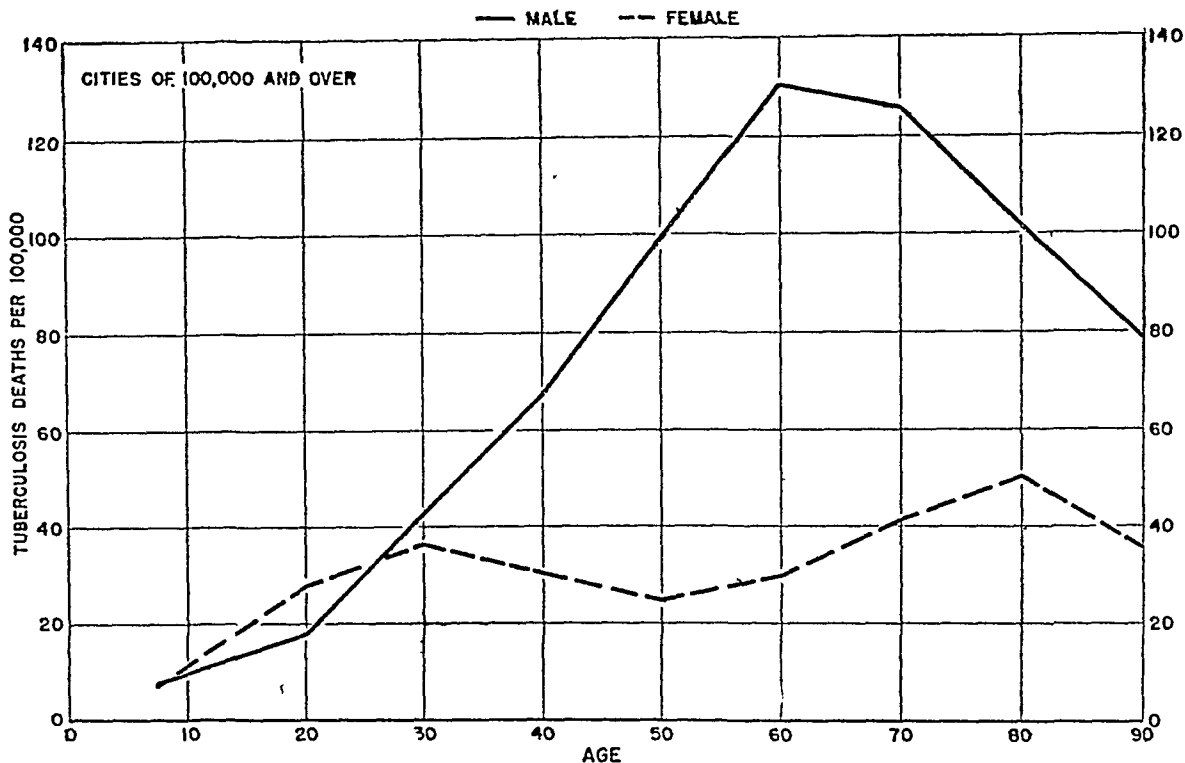


CHART 5. Tuberculosis mortality by age and sex in cities of 100,000 and more population and in rural areas, white population—United States, 1940.

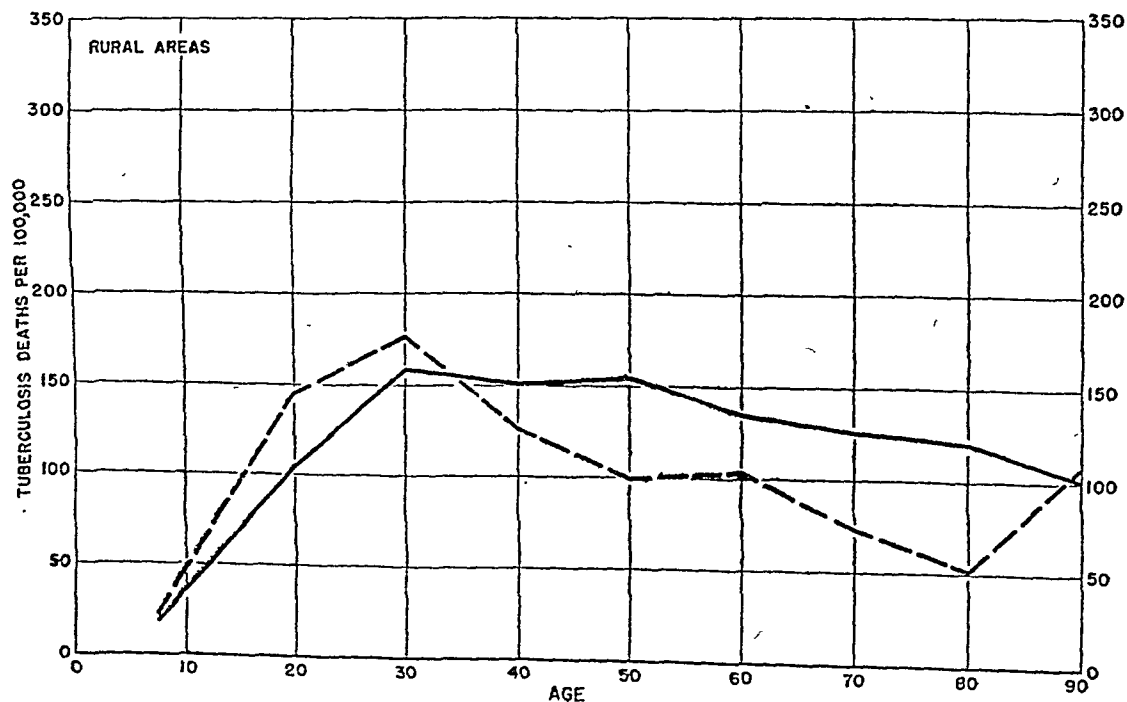
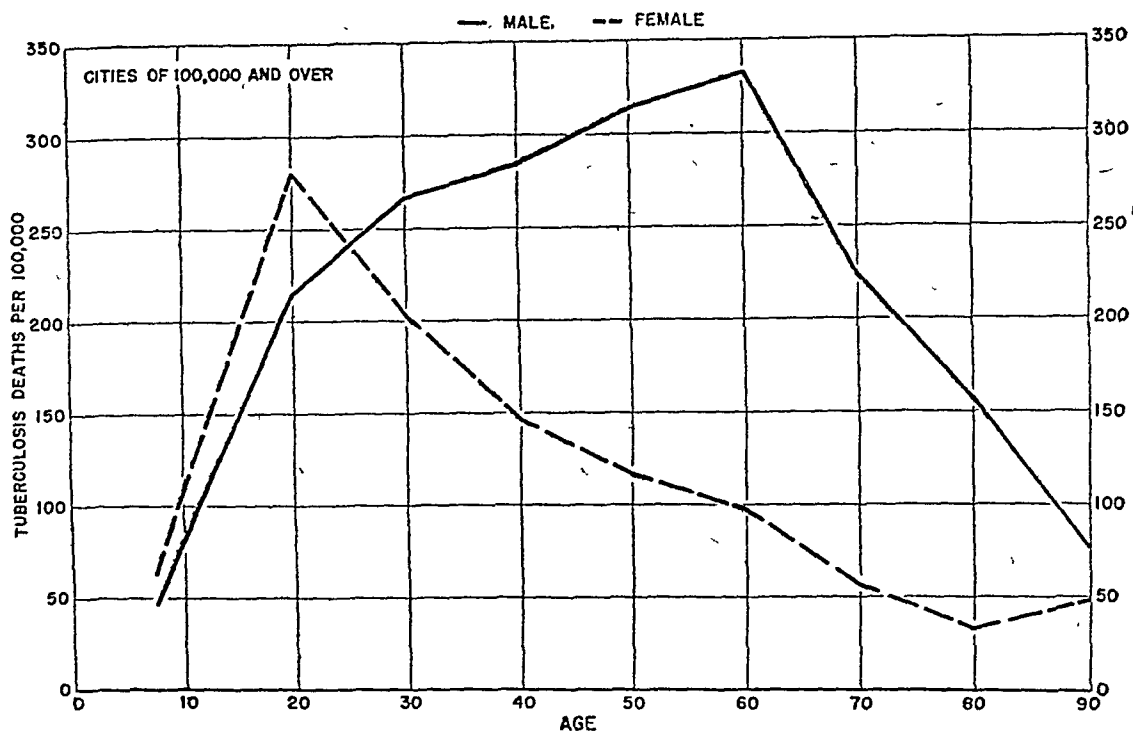


CHART 6. Tuberculosis mortality by age and sex in cities of 100,000 and more population and in rural areas, nonwhite population—United States, 1940.

The factor of fatigue may be operating in the other direction in the case of males to supplement the extrafamilial exposure in producing higher rates for males in large cities. The exertion in urban occupations, particularly in heavy industry, may be greater than in rural occupations. In addition, workers in the cities may not have as many rest periods during the working day as workers in rural occupations have. Another factor to be considered in connection with the higher tuberculosis mortality rates of rural women is their greater fertility. An interesting point in this connection is revealed by charts 5 and 6 which show male and female rates in the large cities and in rural communities for whites and for nonwhites. In urban areas the female tuberculosis death rate for both whites and nonwhites exceeds that of males until age 25, at which time it falls below the rate for males and remains there throughout life. In rural areas this reversal in relationship between female and male rates occurs later, in the early thirties. It may be that the greater fertility of rural women and the associated health risks are responsible for maintaining the high level of tuberculosis mortality for a longer period of time among rural than among urban women.

The assumptions, explanations and indeed the speculations which are made possible by detailed data, such as are presented in this paper, are, of course, numerous. It is to be hoped that future tabulations on tuberculosis by the Bureau of the Census will provide additional necessary details which will open many avenues for the further exploration of many factors which are of importance both from the epidemiological and a practical administrative point of view.

#### SUMMARY

Variations in tuberculosis mortality and in the total death rate in communities of different size are presented by age, sex and race, and the implications of some of these variations are discussed.

The following findings are recorded:

The total death rate is higher in urban than in rural areas in the older ages, but during childhood and adolescence it is more favorable in the large cities.

The tuberculosis mortality rate among males in practically all age groups shows a consistent relationship to size of community. The rate in large cities is considerably higher than in the intermediate-sized cities and the rate in the latter is in turn higher than that of the rural areas. The differences in rates are more pronounced for nonwhites than for whites.

The tuberculosis mortality experience of females is different from that of males. Among white women the death rate is higher in rural areas than in urban areas. The rural rate exceeds the urban rate for females of all ages, except the very youngest. During all other ages, the rate is higher in the country than in the cities.

In the light of the age and sex differences of tuberculosis mortality the following three factors were selected for special discussion:

- 1: Opportunities for exposure to the disease.
- 2: Fatigue, exhaustion, or strain and lack of sufficient rest.
- 3: Fertility.

## SUMARIO

Preséntanse aquí, conforme a edad, sexo, y raza, las variaciones observadas en la mortalidad tuberculosa y en la general en comunidades de diversos tamaños, y discútese el significado de algunas de esas variaciones.

Anótanse los siguientes hallazgos:

La mortalidad total es mayor en las zonas urbanas que en las rurales en las edades más avanzadas, pero más favorable en las ciudades grandes durante la infancia y la adolescencia.

La mortalidad tuberculosa en los varones en casi todos los grupos etarios revela una relación constante con el tamaño de la colectividad, pero siendo en las poblaciones grandes mucho mayor que en las de tamaño intermedio y siendo a su vez en las últimas mayor que en las zonas rurales. Las diferencias en los coeficientes son más pronunciadas para los sujetos no blancos que para los blancos.

La mortalidad tuberculosa en las mujeres es distinta que en los varones, siendo en las blancas mayor en las zonas rurales que en las urbanas y siendo superior en las rurales que en las urbanas para las mujeres a todas edades, salvo en las muy jóvenes.

A la luz de las diferencias de la mortalidad tuberculosa según la edad y el sexo, escogiéronse los tres factores siguientes para estudio:

- 1: Ocasiones de exposición a la enfermedad.
- 2: Fatiga, agotamiento, o tensión y falta de suficiente reposo.
- 3: Fecundidad.

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## VENTILATORY FUNCTION<sup>1</sup>

### Experiences with a Simple Practical Procedure for Its Evaluation in Patients with Pulmonary Tuberculosis

FREDERICK C. WARRING, JR.

From a clinical viewpoint pulmonary function can be divided into two parts, ventilatory and respiratory. Ventilation is concerned with the movement of air into and out of the lungs. Respiration pertains to the gaseous interchange (oxygen and carbon dioxide) which takes place through the walls of the alveoli.

Thus the ventilatory aspect of pulmonary function is mechanical. The major symptom of ventilatory insufficiency is dyspnea.

The respiratory aspect of pulmonary function is largely physio-chemical. The major sign of respiratory insufficiency is cyanosis.

Of course, the ventilatory and respiratory mechanisms are always closely interrelated. Severe ventilatory insufficiency (dyspnea), if progressive, is followed eventually in most instances by respiratory insufficiency (cyanosis). Likewise respiratory insufficiency, by stimulating the respiratory centre in the brain, can increase ventilation. Clinically it is not uncommon to find cases of almost pure ventilatory insufficiency. Cases of pure respiratory insufficiency are also seen, but are rare.

The above discussion is an abstract of the clear and useful classification of pulmonary insufficiency by Cournand and Richards (1). As they emphasized, it is not intended as an analysis of all the complicated interrelations of pulmonary physiology.

Patients having tuberculosis with beginning pulmonary insufficiency generally show first dyspnea alone (ventilatory insufficiency). Dyspnea solely on exercise indicates slight ventilatory insufficiency. Dyspnea even at rest portends serious impairment of pulmonary function. Only when dyspnea becomes persistent and pronounced at rest does cyanosis (respiratory insufficiency) usually make its appearance. Thus, in the majority of patients it appears practical to judge the degree of pulmonary insufficiency by evaluating the ventilatory function alone.

Ventilatory insufficiency results from decrease in the maximum breathing capacity or increase in the breathing requirement, or a combination of both (1).

#### MAXIMUM BREATHING CAPACITY (M.B.C.)

Maximum breathing capacity (also referred to as the maximum ventilatory volume and the maximum minute ventilation) is the maximum volume of air that can be ventilated by the patient in unit time. It is expressed in liters per minute. Maximum breathing capacity has been shown to be a more accurate means of evaluating the patient's ability to ventilate than the vital capacity, which uses only a single breath without regard to time (1).

Determination of the maximum breathing capacity in this study:

<sup>1</sup> From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.

The patient was seated comfortably in a chair. When the maximum breathing capacity was measured in a strict bed patient he was allowed to select his own most comfortable position. Some preferred to sit upright in bed, others to be propped up or to have their legs hanging over the side of the bed. A nose clip prevented any escape of air through the nares. At a signal, the subject began to breath "as hard and as fast as he could" for thirty seconds, through a high velocity, one-way valve<sup>2</sup> into a 100 liter Douglas bag. About two breaths per second was found to be a good rate. A stop watch held before the patient encouraged him to maintain a maximum effort throughout the entire test period. The total expired air in the Douglas bag was measured by passing it through a meter.<sup>3</sup> The result, multiplied by two, gave the maximum breathing capacity in liters per minute. All tests were done at room temperature and corrections were not made for temperature, barometric pressure or humidity. The patient's activities (bathroom, exercise, etc.) at the date of the test were recorded.

Strict attention to certain details was necessary to secure highest and therefore most accurate and uniform readings. A careful check was made for any leaks in the valves or connections. The Douglas bag hung freely on a rack next to the patient, after all air had been expressed from it by rolling it on a flat surface. The importance of the test was stressed to the patient. He was told that the object of the performance was to "blow up the bag as much as he could in half a minute." Reassurance was given that rapid, forced breathing would not harm his pulmonary disease (no spreads of tuberculosis were observed following more than 500 tests). If possible a new patient watched an experienced one perform. The presence of 2 patients in the room at the same time encouraged competition. The operator sometimes demonstrated with a few breaths himself how hard and fast he wanted the patient to breathe. The patient was permitted to try a few practice breaths through the valve before it was connected to the Douglas bag. Care was taken that the nose-piece was on snugly and that the patient did not allow air to leak around the mouthpiece. Too rapid, too slow or irregular breathing was not desirable—otherwise the patient was encouraged to set his own pace. It was sometimes helpful to mark time with his breathing. The subject was constantly encouraged to strong effort during the entire thirty seconds test period. He was usually able to judge himself if his trial was the best possible. If either the patient or the operator felt that a better effort could be made, the test was repeated after resting or on another day. When both were satisfied the result was accepted. Results were reproducible within 5 liters. By having a single operator conduct all of the tests it was felt that results were more uniform and comparable.

<sup>2</sup> This valve must satisfy several criteria. It must allow expired air to go into but not out of the Douglas bag. Its inside diameter must be large enough so that there is no resistance to rapid breathing. It should be so constructed that it can be cleaned readily. The high velocity valve used in this work was made by Hans Rudolph, 5719 Kenwood, Kansas City, Missouri.

<sup>3</sup> An inexpensive, converted gas meter is available from the Arthur H. Thomas Company, Philadelphia. Many local illuminating gas companies are able to check its calibration.

Normal mean values for maximum breathing capacity are 154 liters per minute in men and 100 liters per minute for women (1).

The mechanics of ventilation is composed of five principal factors—the functions of the ribs, diaphragms, pleurae, lung parenchyma, and bronchi. Their modes of function are well described by Best and Taylor (2).

These various ventilatory factors are, of course, interrelated and impairment of function of one may secondarily affect one or more of the others. Thus adhesive pleuritis, besides destroying ability of the pleurae to glide over each other, may secondarily restrict motion of the ribs and diaphragm.

Any impairment of ventilatory function by disease or injury is manifested by a lowering of the maximum breathing capacity. Likewise collapse therapy, by altering any of these factors of ventilation, may change the maximum breathing capacity.

#### BREATHING REQUIREMENTS

Breathing requirement is the ventilation in liters per minute in any given physical state. This volume is regulated by reflex stimulation of the respiratory center and varies with the state of metabolism, posture, exertion, anoxia of the blood and tissues, emotional and other nervous states (1).

At rest in bed, patients with tuberculosis were found to ventilate 5 to 12 liters per minute.

This study began as an attempt to evaluate patients' ventilatory function by using only the maximum breathing capacity to demonstrate total ventilatory ability, together with differential bronchspirometry to indicate the proportion of function in the two lungs. The question soon arose as to what was the lowest maximum breathing capacity with which a patient could be left after any given collapse procedure. At first 25 liters per minute was set as the minimum below which the maximum breathing capacity could not be safely reduced. It then appeared that, whereas one patient could move around comfortably with a maximum breathing capacity of 25 liters per minute, others were quite dyspneic at this same level.

A means was sought to evaluate the adequate breathing requirement of each individual patient. The breathing requirement at rest was not the entire answer, since it was desirable to have the patient ambulatory after a collapse procedure. Therefore a simple test was developed to determine the ventilation per minute while walking on the level at a slow, uniform pace. This was designated the *walking ventilation* (W.V.) and will be described in detail later.

Several interesting facts about the walking ventilation appeared. It varied in volume from 8 to 30 liters per minute in different patients. Next, a definite correlation was found between the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  and the degree of dyspnea present when walking. Finally, and most remarkable, in the majority of patients the walking ventilation remained constant for any one patient over periods of observation as long as twenty-two months. Since the walking ventilation remained constant it could be utilized as a base line for

the present and future breathing requirements of any individual patient. How the walking ventilation was used with the maximum breathing capacity to evaluate ventilatory ability and to control collapse therapy will be shown.

Walking ventilation was measured by using the same apparatus that was described for the maximum breathing capacity. The nose clip was applied. The operator and patient then walked slowly and uniformly, side by side, over a measured level course (a hallway suited the purpose), covering 180 feet in one minute. Checking the distance every fifteen seconds maintained an even pace. For the first minute the patient walked without holding the valve or breathing into the Douglas bag. Immediately following this "warming-up period" the subject walked for three more minutes, holding the valve and breathing into the bag which was carried by the operator. The patient was encouraged to "breathe naturally, just as you always do when you walk." Just as soon as the test was completed, the nose clip was removed and the subject was immediately asked whether he was not dyspneic; slightly dyspneic (just noticed labored breathing); moderately dyspneic (uncomfortable breathing but could continue); or severely dyspneic (exhausted—unable to continue). The degree of dyspnea was then recorded. The total expired air in the Douglas bag was passed through the gas meter and the result, divided by three, gave the walking ventilation in liters per minute.

Here, as in the measurement of the maximum breathing capacity, the performance had to be done carefully if results were to be accurate and uniform. The apparatus was again checked for leaks. The patient was made to understand that he should not try to breathe too hard or too easily, but just naturally. It was even better if he could forget about the breathing and think about something else. It was necessary to watch out for a tendency for the respiratory rate to keep time with the footsteps. Care was taken that the patient's lips were closely applied to the mouthpiece. Sometimes at the conclusion of the walking test differentiation had to be made between a feeling of fatigue and a sense of dyspnea. Dyspnea was explained to the patient as "labored breathing." Occasionally a patient who was obviously dyspneic denied the sensation. In those few instances slight dyspnea was recorded.

The walking ventilation test can be performed by any patient strong enough to walk to the bathroom. The measurements were reproducible within 3 liters.

The walking ventilation in the majority of patients remained relatively constant for any one individual. This was so with improvement or spread of disease, before and after induction and reexpansion of pneumothorax, and before and after thoracoplasty.<sup>4</sup>

<sup>4</sup> A standard exercise test consisting of stepping up and down a step 20 centimeters high thirty times in one minute was used by Cournand and Richards (1). Ventilation was observed during the test and in the period of recovery which was limited to five minutes following the cessation of exercise. The walking ventilation test is similar in principle but is easier to perform and more nearly duplicates the patient's normal exercise. Results of the walking ventilation test confirm correlations between breathing reserve and dyspnea on exercise as observed by Cournand and Richards.



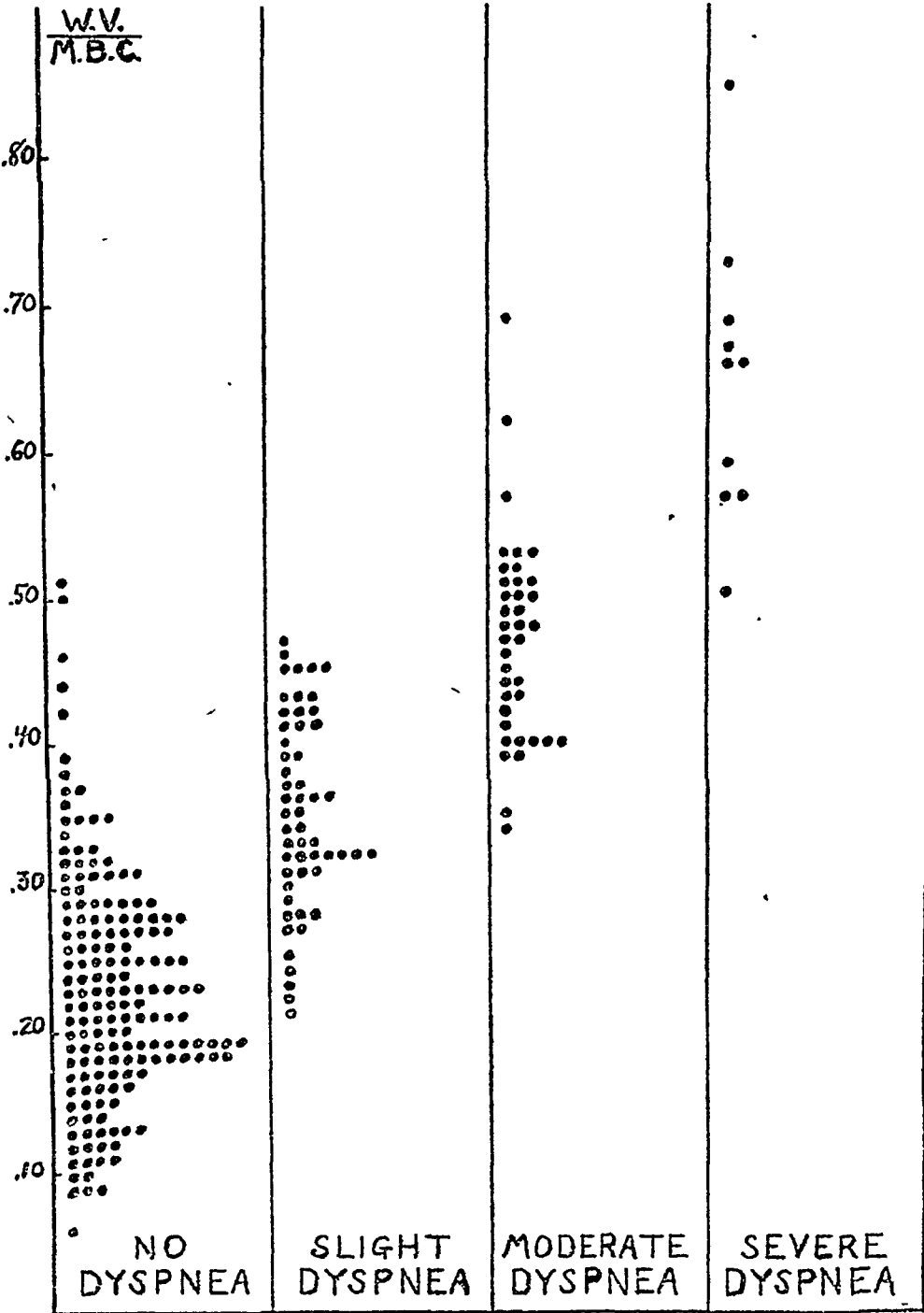


CHART 1. See text.

As long as the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  in a given patient was below 0.30 the patient was usually not dyspneic when walking on the level. However,

as the value of the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  increased, dyspnea became more prominent, in this manner:

When the ratio  $\frac{\text{Walking Ventilation}}{\text{Maximum breathing capacity}}$  was around 0.35 slight dyspnea was present.

When the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  was around 0.45 moderate dyspnea was present.

When the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  went over 0.50 severe dyspnea was present at the end of the walking test.<sup>5</sup>

Chart 1 shows the correlation between the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  and dyspnea on walking in 268 determinations on 167 subjects. These patients had all types and degrees of tuberculosis and were receiving various forms of therapy, including bed-rest. Some were improving, others were becoming worse. The observations in the four groups (no dyspnea, slight dyspnea, moderate dyspnea and severe dyspnea) in chart 1 were studied by statistical methods. The difference between the means of one group and any other group is highly significant.

#### USE OF THE RATIO $\frac{\text{WALKING VENTILATION}}{\text{MAXIMUM BREATHING CAPACITY}}$ IN THORACOPLASTY

Everyone treating tuberculosis is anxious to avoid the use of any collapse therapy that will make the patient a respiratory invalid. This is especially so

<sup>5</sup> Cournand and Richards stress the concept of *breathing reserve*. The excess breathing capacity beyond actual ventilation in any given physical state is the breathing reserve (1). Thus in a patient whose maximum breathing capacity = 150 liters per minute and whose walking ventilation = 20 liters per minute, the breathing reserve is 130 liters per minute.

They have shown the correlation between the ratio  $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$  and dyspnea. To have employed this concept in the present paper would have meant using the ratio

$\frac{\text{Maximum breathing capacity—walking ventilation}}{\text{Maximum breathing capacity}} \times 100$ . The ratio

$\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  has been used because of its greater simplicity for our particular purposes. The values of the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  are in inverse proportion to those of the ratio  $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ . Thus a patient whose

ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  is 0.35 has a ratio  $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$  of 65 per cent.

Thus a patient whose ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  is 0.35 has a ratio  $\frac{\text{Maximum breathing capacity—walking ventilation}}{\text{Maximum breathing capacity}} \times 100$  of 65 per cent.

where an irreversible procedure such as thoracoplasty is contemplated. After collapse therapy a patient should be able at least to walk slowly on the level without uncomfortable dyspnea. It is shown in chart 1 that severe dyspnea

occurred when the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  was over 0.50. Since the walking ventilation tended to remain constant in a large majority of patients receiving the usual types of therapy (bed-rest, pneumothorax, phrenic, thoracoplasty), it was felt that collapse therapy must not reduce the maximum breathing capacity below twice the value of the patient's walking ventilation (that is, the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  must not exceed 0.50) if the patient was to avoid becoming a respiratory invalid.

*Method:* Before operation the patient's maximum breathing capacity and walking ventilation were determined. At the same time motion of the ribs and diaphragm and mediastinal shift were observed under the fluoroscope. If pneumothorax was present the degree of parenchymal expansion on inspiration was noted. Rib and diaphragm motions were recorded as estimated percentage of normal. If the maximum breathing capacity was 70 liters per minute or greater, and if by fluoroscopy motion of the ribs and diaphragm was good on the side opposite operation, then differential bronchspirometry was not considered necessary. Otherwise bronchspirometry was used to complete the picture in border-line cases (desirable in only one-fourth of the candidates for thoracoplasty).

Considered as border-line cases were:

- 1: Patients with a maximum breathing capacity over 70 liters per minute, but whose rib and diaphragm motions were better on the side of operation than on the contralateral side.
- 2: Patients with a maximum breathing capacity slightly below 70 liters per minute, with some motion of the ribs and diaphragm on the side of operation, and who needed extensive thoracoplasty.
- 3: Patients with a low maximum breathing capacity, around 50 liters per minute, but with no functioning lung evident on the side of operation (reoperation, complete collapse by pneumothorax).
- 4: Patients with a lowered maximum breathing capacity who might tolerate and benefit by a limited apical thoracoplasty.

The maximum breathing capacity was repeated in bed thirteen days after each stage in 9 cases studied. Further surgery was avoided when it was felt that it might reduce the maximum breathing capacity more than a few liters below two times the value of the preoperative walking ventilation. In no event was the maximum breathing capacity allowed to fall below 25 liters per minute.

After complete recovery from operation final evaluation of the patient's ventilatory function was made, usually when he had completed one hour outside walking exercise twice a day. This was reached from six to twelve months after the last stage and all patients by that time had pretty well regained their muscle tone. The maximum breathing capacity, walking ventilation, and fluoroscopic examinations were repeated. Differential bronchspirometry was not done again.

CHART 2. Changes in the maximum breathing capacity and the walking ventilation following thoracoplasty.  
 In each pair the upper, or white block shows the change in the maximum breathing capacity and the lower, solid block shows the change in the walking ventilation after thoracoplasty. All changes are decreases after thoracoplasty, except where increases are indicated by arrows.

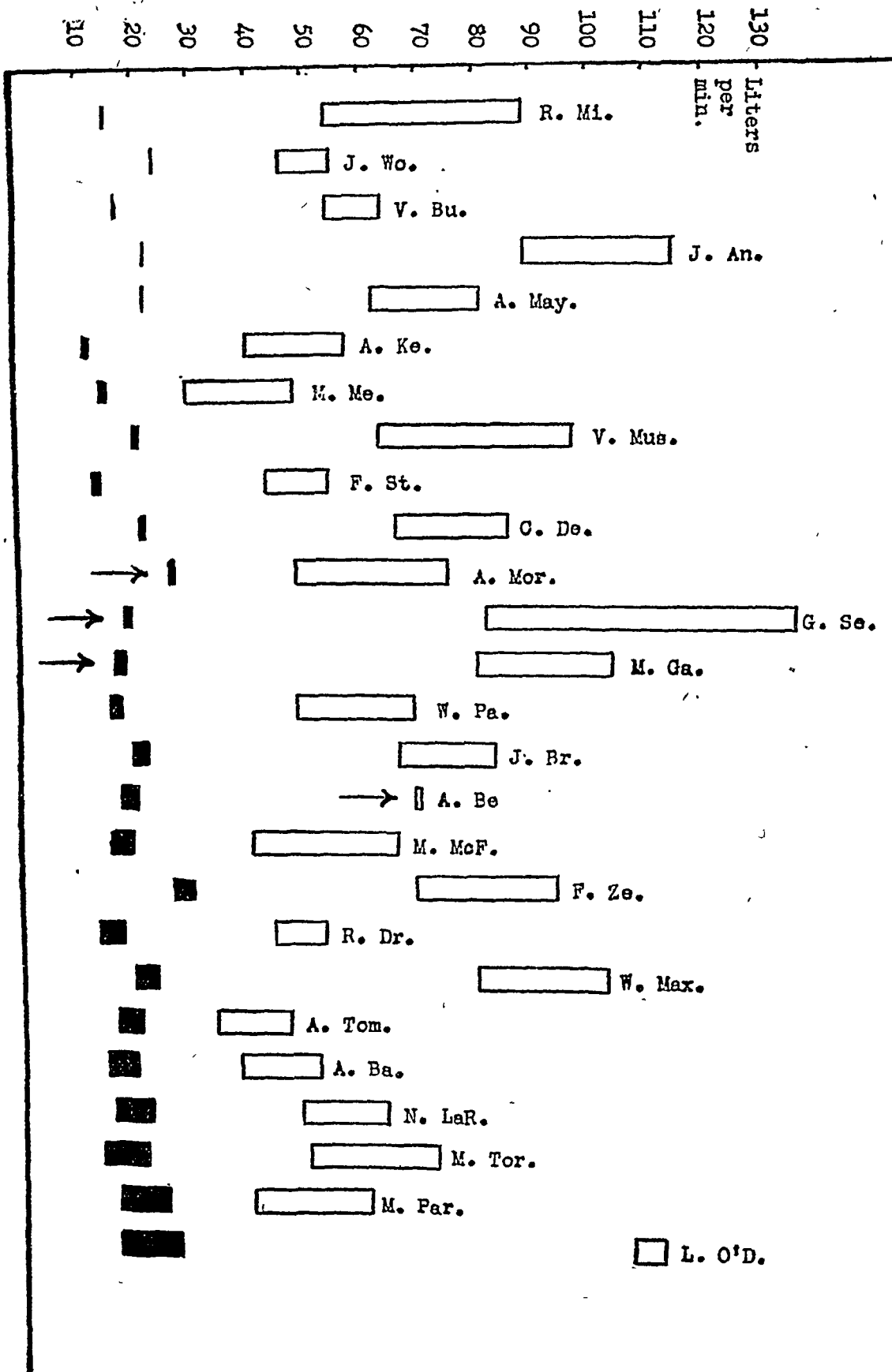


TABLE 1

*Changes in ventilatory function following thoracoplasty*

		K.B.C.	W.V.	W.V. H.B.C.	DYSPNEA ON WALKING	PRIVILEGES	MOTION ON SIDE OF OPERATION		FUNCTIONING LUNG COLLAPSED	REMARKS
							Ribs	Diaphragm		
J. An., white male 48	R. 8 ribs	Before After	22 89	0.19 0.25	0 0	Full bathroom priv. Full bathroom priv.	50% 20%	50% 50%	+	Previous right pneumothorax with fluid. Complete reëxpansion before first test.
	L. 8 ribs	Before After	52 38	0.37 0.37	slight 0	Full bathroom priv. One hour inside exer.	25% 0	0 0	0	Bronchspirometry: left—O <sub>2</sub> = 0%; ventilation = 0%
A. Be., white female 30	R. 11 ribs	Before After	69 70	0.29 0.24	0 0	Full bathroom priv. One hour outside exer.	? 0	0 20%	+	At first test—right pneumothorax (50% collapse) and right temporary phrenic.
	L. 11 ribs	Before After	83 66	0.27 0.29	0 slight	Two walks to bath- room One hour outside exer.	75% 0	0 50%	0	At first test—left pneumothorax (90% collapse), fluid and left temporary phrenic. Fluid absorbed at time of second test.
V. Bu., white female 20	L. 9 ribs and ant. stage	Before After	64 54	0.27 0.31	0 0	Full bathroom priv. One hour outside exer.	? 0	0 50%	+	At first test—pneumoperitoneum and left temporary phrenic.
	R. 8 ribs	Before After	86 66	0.26 0.32	0 0	Full bathroom priv. One hour outside exer.	50% 25%	50% 75%	+	
R. Dr., white female 26	L. 11 ribs	Before After	53 44	0.32 0.30	slight slight	Full bathroom priv. One hour outside exer.	20% 0	0 0	0	At first test—left pyopneumothorax, with bronchopleural fistula (90% col- lapse).

M. Ga., white male 49	L. 8 ribs	Before After	104 80	16 18	0.15 0.23	0 0	Full bathroom priv. ½ hour outside exer.	25% 0	0 0	0	At first test—left pneumothorax; no motion. Bronchspirometry: left—O <sub>2</sub> = 4%; ventilation = 5%.
A. Ke., white female 50	R. 5 ribs and scapu- lect'y	Before After	57 40	12 11	0.21 0.23	0 slight	Full bathroom priv. One hour inside exer.	50% 50%	0 30%	0	At first test—right temporary phrenic. Collapse controlled by M. B. C. be- tween stages.
N. LaR., white female 23	R. 8 ribs	Before After	64 49	22 15	0.34 0.31	0 0	Full bathroom priv. Working on ward.	50% 0	25% 10%	0	Bronchspirometry: right—O <sub>2</sub> = 43%; ventilation = 44%.
A. May., white male 24	R. 8 ribs	Before After	81 62	22 22	0.27 0.35	0 slight	Full bathroom priv. One hour outside exer.	? 30%	? 50%	+	Previous right pneumothorax, with fluid. Complete reëxpansion before first test.
W. Max., colored female 32	L. 8 ribs	Before After	103 80	23 19	0.22 0.24	0 0	Full bathroom priv. ½ hour outside exer.	? 25%	100% 100%	+	Previous left pneumothorax. Complete reëxpansion before first test.
M. McF., white male 45	L. 8 ribs	Before After	66 40	19 15	0.29 0.38	slight slight	Full bathroom priv. One hour outside exer.	50% 10%	0 0	+	Permanent left phrenic.
M. Me., white female 29	L. 8 ribs	Before After	48 29	15 14	0.31 0.48	0 slight	Full bathroom priv. ½ hour outside exer.	? 0	25% 30%	+	At first test—pneumoperitoneum and left temporary phrenic.
R. Mi., colored female 25	L. 8 ribs	Before After	89 54	15 15	0.17 0.28	0 0	Full bathroom priv. One hour outside exer.	50% 0	0 0	++	Permanent left phrenic.
A. Mor., white female 54	R. 11 ribs	Before After	75 48	26 27	0.35 0.56	0 severe	Full bathroom priv. ½ hour inside exer.	? 0	25% 50%	+	..
V. Mus., colored female 29	R. 8 ribs	Before After	97 63	21 20	0.22 0.32	0 0	Full bathroom priv. One hour outside exer.	100% 20%	75% 75%	++	

TABLE 1—Continued

		M.B.C.	W.V.	M.B.C.		DYSPNEA ON WALKING	PRIVILEGES	MOTION ON SIDE OF OPERATION		FUNCTIONING LUNG COLLAPSED	REMARKS
				W.V.	M.B.C.			Ribs	Diaphragm		
L. O'D., white male 17	L. 8 ribs	Before	113	27	0.24	0	Full bathroom priv. One hour outside exer.	?	?	0	At first test—Left pyopneumothorax, apex to fifth rib (50% collapse). Thickened pleura on left.
		After	108	16	0.15	0		10%	70%		
W. Pa., white male 30	L. 7 ribs	Before	69	17	0.25	0	Full bathroom priv. One hour outside exer.	50%	0	+	Left permanent phrenic. Bronchospir- ometry: left—O <sub>2</sub> = 40%; ventilation = 36%.
		After	48	15	0.31	slight		10%	0		
M. Par., white female 40	R. 11 ribs	Before	61	25	0.41	slight	1 walk to bathroom One hour outside exer	?	50%	+	Previous right pneumothorax. Com- plete reexpansion before first test.
		After	40	16	0.40	mod- erate		0	0		
G. Se., white male 32	L. 8 ribs	Before	136	18	0.13	0	Full bathroom priv. One hour outside exer.	75%	100%	++	Previous left pneumothorax. Complete reexpansion before first test.
		After	82	19	0.23	0		15%	75%		
F. St., white female 45	L. 8 ribs	Before	54	14	0.26	0	Full bathroom priv. Working.	?	25%	+	Before first test—three left temporary phrenics.
		After	43	13	0.30	0		0	25%		
A. Tom., white male 48	R. 11 ribs	Before	47	20	0.43	slight	Full bathroom priv. Working.	50%	0	0	At first test—right pyopneumothorax (80% collapse).
		After	34	16	0.47	slight		0	0		
M. Tor., white female 47	R. 8 ribs	Before	73	21	0.29	0	Full bathroom priv. Light housework.	?	50%	+	Previous right pneumothorax. Com- plete reexpansion before first test. Previous right temporary phrenic.
		After	50	13	0.26	0		20%	75%		

J. Wo., white male 36	L.	Before		24		0.44		0	$\frac{1}{4}$ hour inside exer. One hour outside exer.		0	0	0	0	Revision of old eleven rib thoracoplasty
		After	After	46	24	0.52	0								
F. Ze., white male 40	L. 11 ribs	Before	94	30	0.32	0	Full bathroom priv. $\frac{1}{4}$ hour outside exer.	0	25% 0	25% 0	+	0	0	0	Previous left pneumothorax, with fluid. Reexpansion at time of first test, with some fluid persisting. Left permanent phrenic done after thoracoplasty to assist in control of fluid. Fluid com- pletely absorbed at time of second test.
		After	69	26	0.38	0									

Functioning lung collapsed: 0 = none or very little.

+ = moderate.

++ = much.

M.B.C. = maximum breathing capacity.

W.V. = walking ventilation.



*Results:* Twenty-six patients have been studied before and after thoracoplasty by this method. Changes in maximum breathing capacity and walking ventilation after operation in these cases are shown in chart 2. Lowering of the maximum breathing capacity following operation occurred in 25 of the 26 cases—in many patients materially and in a few the drop was as high as 30 or 40 liters.

In only 5 patients did the walking ventilation change 5 liters or more following thoracoplasty. Thus in 21 of the 26 cases (81 per cent) the walking ventilation remained sufficiently constant before and after operation to provide a base-line for the estimation of the patient's breathing requirement.

Details pertaining to these 26 thoracoplasties are presented in table 1. The large majority of these thoracoplasties were eight ribs or more, with long sections of the ribs being removed.

TABLE 2  
*Changes in the M.B.C. following thoracoplasty stages*

	BEFORE THORO- COPLASTY	AFTER				RECOVERY	
		1st stage	2d stage	3d stage	4th stage	with exercise	come-back in liters
A. Ba.....	52	?	44	32	—	38	+6
C. De.....	86	106	87	59	—	66	+7
				Scapu- lectomy			
A. Ke.....	57	44	34	37	—	40	+3
N. LaR.....	64	52	42	34	—	49	+15
E. Ma.....	66	69	57	49	—	54	+5
M. McF.....	66	?	?	29	—	40	+11
R. Mi.....	89	77	?	48	—	54	+6
V. Mus.....	97	?	68	58	—	63	+5
A. Tom.....	47	40	39	36	30	34	+4

In table 2 are shown the changes in the maximum breathing capacity following stages of thoracoplasty, and at the completion of the recovery period, in 9 patients. It did not seem that any one stage uniformly depressed the maximum breathing capacity more than any of the others. Nor did it seem possible to predict with certainty how much a stage would affect the maximum breathing capacity. These variations are probably related to the location and extent of the disease on the side being collapsed and to the degree in which good functioning lung tissue was compressed. It was expected that, in comparison with the maximum breathing capacity done in bed soon after the last stage, there would be an appreciable return of function when the patient later resumed exercise. However, 7 of the 9 patients each regained only 7 liters or less upon recovering their muscle tone, while one improved by 11 and the ninth by 15 liters. Thus in extensive thoracoplasties of eight or more ribs it was not found feasible to expect more than 7 liters recovery in the maximum breathing capacity after the last stage operation.

## VENTILATORY FUNCTION IN OTHER TYPES OF THERAPY

Study of ventilatory function was found useful in following various states of pulmonary tuberculosis and their reaction to other kinds of therapy.

On bed-rest alone the maximum breathing capacity tended to increase with clearing of disease and improvement of muscle tone and to decrease with progression of tuberculosis or loss of muscle tone brought on by bed-rest. In these cases the walking ventilation remained constant in the majority of patients for as long as a year and a half.

Only a few temporary phrenicectomies were studied. Wright and Woodruff have found that temporary phrenicectomy without thoracoplasty does not materially affect the maximum breathing capacity (3). The results in our patients tended to support this conclusion. Even though, as Wright and Woodruff suppose, the homolateral ribs and contralateral lung may compensate to maintain function after temporary phrenicectomy, we have preferred not to do a temporary phrenicectomy if, before operation, the maximum breathing capacity was already lowered to the extent where the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  approached 0.50. Walking ventilation showed no change after temporary phrenicectomy.

Six patients were studied before and after inducing pneumothorax and 2 others before and after beginning pneumoperitoneum. There was no appreciable change in the walking ventilation in 4 of the 6 pneumothorax patients and in both cases of pneumoperitoneum.

It was found that selective, uncomplicated pneumothorax did not materially reduce the maximum breathing capacity. In one patient the ventilatory function was actually improved after selective collapse was established. On the other hand, when it became necessary to increase the degree of collapse (to attempt cavity closure) so that good, functioning lung parenchyma was compressed, there was concomitant lowering of the maximum breathing capacity. In instances where collapse was producing dyspnea, the degree of the pneumothorax could be controlled by watching the maximum breathing capacity. Pneumothorax was not pushed beyond the point where the ratio

$\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  exceeded 0.50. In this manner dangerous dyspnea was avoided.

There was no appreciable change in the maximum breathing capacity of the 2 patients before and after induction of pneumoperitoneum. Both had paralyzed diaphragms from temporary phrenicectomies.

Thirteen additional cases of pneumothorax were observed before and after reëxpansion and 2 more patients before and after abandoning pneumoperitoneum. The walking ventilation remained constant in 11 of these pneumothorax cases and in both of the patients who received pneumoperitoneum. Ten of the patients increased their maximum breathing capacity 5 liters or less following reëxpansion of pneumothorax. In fact in 2 instances there was a slight decrease in the maximum breathing capacity when the collapsed lung was allowed out.



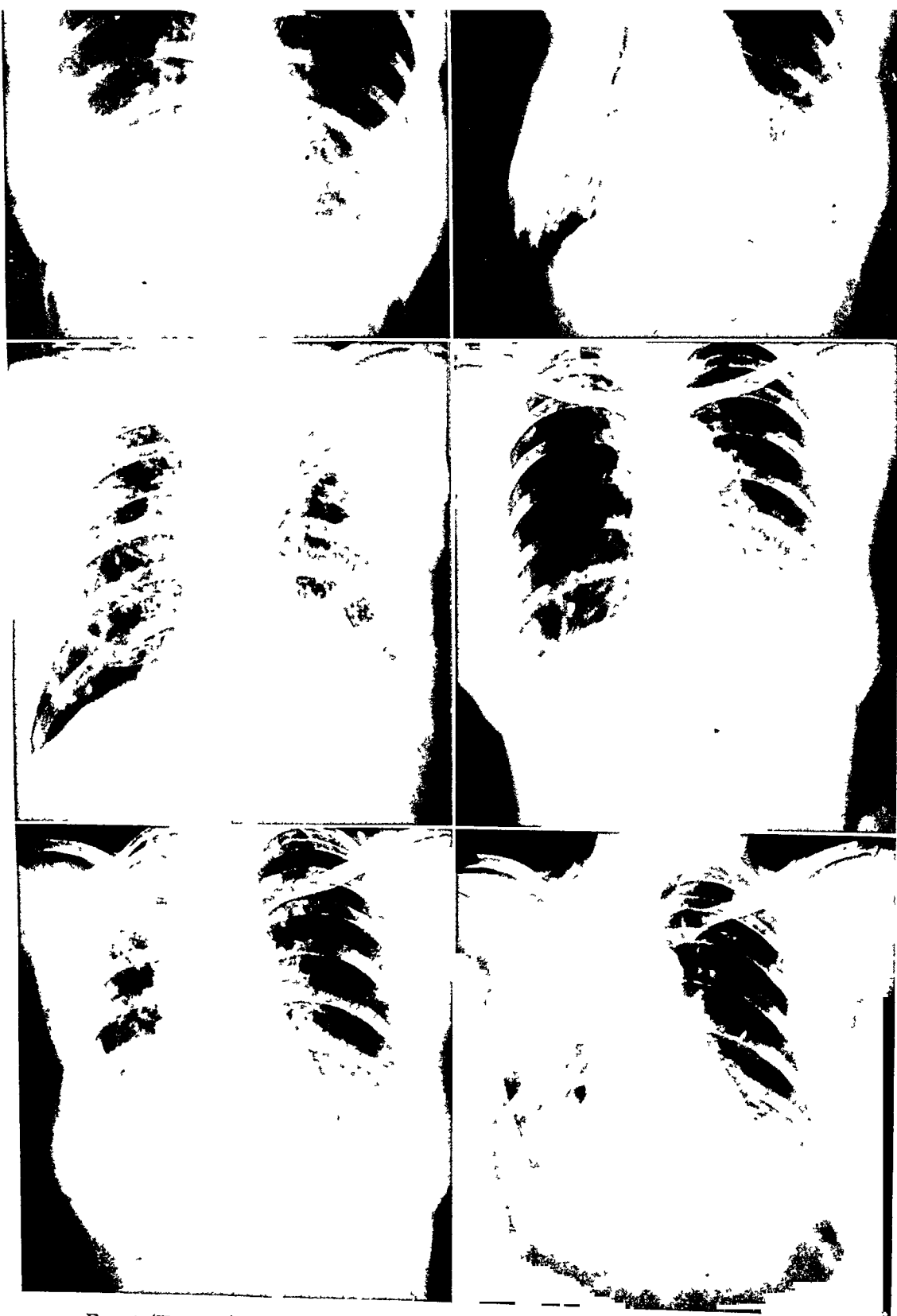


FIG. 1 (Top left), FIG. 2 (Top right), FIG. 3 (Centre left), FIG. 4 (Centre right),  
FIG. 5 (Bottom left), FIG. 6 (Bottom right)

plasty to 63 liters per minute after operation. This marked drop of 34 liters is probably related to the fact that a large area of functioning lung, along with the diseased apex, was collapsed by the thoracoplasty. Walking ventilation remained constant before and after operation.

*Case 2:* W. Sh. White male, age 51. Admitted in December, 1940, with far advanced pulmonary tuberculosis involving all lobes. Sputum positive. On bed-rest he showed clinical improvement and some clearing of the disease according to X-ray films. Because of residual cavities in the left apex a left temporary phrenicectomy was done in February, 1943 and resulted in paralysis. The motion of the left hemidiaphragm was markedly impaired by an old fibrinous pleurisy even before phrenicectomy. Cavities on the left and positive sputum persisted. Left apical thoracoplasty was considered in December, 1943. At that time he was a good chronic. He experienced no dyspnea on the ward, but had moderate dyspnea when on outside exercise. X-ray films showed scattered mottling and fibrosis throughout the right lung, with no cavity. On the left there was scattered mottling and fibrosis throughout with several cavities in the upper lobe. There was fibrinous pleurisy of the left diaphragm (figure 3). Ventilatory studies in December, 1943:

One hour outside exercise twice a day.

Maximum breathing capacity = 35 liters per minute.

Walking ventilation = 18 liters per minute  $\left( \frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}} = 0.51 \right)$ .

Dyspnea after walking ventilation = none.

Fluoroscopy: Right: ribs—30 per cent motion,  
diaphragm—100 per cent motion.

Left: ribs—20 per cent motion,  
diaphragm—no motion.

Although the patient claimed he was not dyspneic after walking, his

$\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  ratio was 0.51. Even an upper lobe thoracoplasty would probably further reduce the maximum breathing capacity, increase the ratio

$\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  and result in uncomfortable dyspnea. Patient was rejected for left thoracoplasty. Case may be reconsidered later if motion of the left diaphragm returns. With the old fibrinous pleurisy little diaphragmatic motion may return and it is questionable, if it does, whether the maximum breathing capacity will be improved.

*Case 3:* A. Ke. White female, age 50. Very ill when admitted to Laurel Heights, February, 1941. There was dense infiltration on the right to the second rib and fibrosis from the second rib to the base. At the right apex was a 3 cm. cavity. On the left was scattered, fine, proliferative disease with slight thickening of the pleura. Positive sputum. A right temporary phrenicectomy in November, 1941 resulted in paralysis but the cavity persisted. Right pneumothorax was instituted in January, 1942. Although the right lung was adherent at the apex, the sputum was negative on concentration in June and July, 1942. Sputum became positive again in August, 1942 and a right temporary phrenicectomy was again performed in September, 1942 without converting the sputum. This was her ventilatory status in November, 1942, with right pneumothorax supplemented by right temporary phrenicectomy (figure 4):

Full bathroom privileges.

Maximum breathing capacity = 36 liters per minute.

Walking ventilation = 12 liters per minute  $\left( \frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}} = 0.33 \right)$ .

Dyspnea after walking ventilation = slight.

Right pneumothrax was abandoned as unsatisfactory and complete reëxpansion of the lung occurred by January, 1943 (figure 5). Cavity persisted at the right apex. Her ventilatory function had improved:

Full bathroom privileges.

Maximum breathing capacity = 57 liters per minute.

Walking ventilation = 12 liters per minute  $\left( \frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}} = 0.21 \right)$ .

Dyspnea after walking ventilation = none.

Fluoroscopy: Right: ribs—50 per cent motion.

diaphragm—no motion.

Left: ribs—100 per cent motion.

diaphragm—100 per cent motion.

An attempt at differential bronchspirometry failed because of the marked distortion of the lower trachea. It was decided to go ahead with right thoracoplasty, measuring the maximum breathing capacity after each stage and stopping if her ventilatory function should become endangered. This is how she responded to her operations:

May 6, 1943—first stage right thoracoplasty—two ribs.

May 19, 1943—maximum breathing capacity = 44 liters per minute.

May 27, 1943—second stage right thoracoplasty—three more ribs.

June 2, 1943—maximum breathing capacity = 32 liters per minute.

June 23, 1943—maximum breathing capacity = 39 liters per minute.

July 14, 1943—maximum breathing capacity = 34 liters per minute.

It was possible that further removal of ribs might reduce the maximum breathing capacity to a point where the patient would be uncomfortably dyspneic (that is, the

ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  might approach 0.50). The patient and her family

strongly preferred to avoid more than slight dyspnea. Therefore it was decided to forego further removal of ribs and a right partial scapulectomy was done on July 15, 1943.

July 28, 1943—maximum breathing capacity = 37 liters per minute.

Convalescence was uneventful. She reached one hour inside exercise twice a day by February, 1944. Her ventilatory picture then was (figure 6):

Privileges—one hour inside walking exercise twice a day.

Maximum breathing capacity = 40 liters per minute.

Walking ventilation = 11 liters per minute  $\left( \frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}} = 0.28 \right)$ .

Dyspnea after walking ventilation = slight.

Fluoroscopy: Right: ribs—50 per cent motion,

diaphragm—30 per cent motion.

Left: ribs—50 per cent motion,

diaphragm—100 per cent motion.

Although the patient's sputum remained positive on concentration, she was discharged as a stable, good chronic. Her respiratory function was adequate. Had this patient's family been less concerned about possible dyspnea, two more ribs might have been removed without dangerously impairing the ventilatory function.

In spite of the dense infiltration in the apex of the right lung of this patient, the remainder of this lung evidently contributed materially to the total ventilatory function, so that removal of only five ribs reduced the maximum breathing capacity 17 liters. It is remarkable how constant the walking ventilation remained over fifteen months, during which time the patient underwent several changes of therapy. Finally, scapulectomy, as expected, did not affect the maximum breathing capacity.

#### DISCUSSION

In 25 of the 26 thoracoplasty cases studied at Laurel Heights the maximum breathing capacity was reduced by operation—in many instances materially and in a few by as much as 30 liters per minute or more. Wright and Woodruff (3) have studied a group of patients on whom selective apical thoracoplasties were done. In several of their cases no reduction of the maximum breathing capacity was found following operation and improvement of the ventilation occurred in a few. It is probable that the frequent and often appreciable reduction of the maximum breathing capacity in our series was related to a more extensive type of operation. Twenty-three of our 26 thoracoplasties were of eight or eleven ribs, with long sections of the ribs being removed. When thoracoplasty of such extent is performed there is more chance that good functioning lung will be collapsed and that the motion of the diaphragm will be impeded on the side of operation.

In addition, in my opinion, it is quite possible that the long-term postoperative application of tight pressure binders adversely affected the final ventilatory function in some cases. All of these thoracoplasty patients wore tight binders completely encircling the entire thorax from the time of wound healing to six months postoperatively. That such a binder restricts rib motion on the "good" side is apparent. Application of pressure did, in fact, cause rather distressing dyspnea in a few patients with low ventilatory function; this dyspnea could be relieved promptly by removal of the binder.

Unless such adverse influence by application of postoperative pressure is assumed, it is difficult to explain the reduction of total function by thoracoplasty in 4 patients (J. Br., R. Dr., A. Tom., and J. Wo.). Preoperatively the first 3 of these patients each had chronic pyopneumothorax, with complete collapse of the lung. The fourth underwent a slight revision of an old eleven-rib thoracoplasty. It was not expected that operation would materially lower the maximum breathing capacity in any of these cases, yet the ventilatory function was reduced 17, 9, 13 and 9 liters per minute, respectively. It is possible that long-term application of pressure contributed to the reduction of the maximum breathing capacity in these cases by permanently impairing the function of the ribs on the "good" side.

It was shown in table 2 that recovery in the maximum breathing capacity after the last stage operation was limited to 7 liters or less in the majority of patients studied. It is difficult to understand why a patient (R. Mi.) with a maximum breathing capacity of 48 liters per minute in bed, thirteen days after her third stage operation, should have recovered only 6 liters, to reach 54 liters

per minute when on exercise nine months later. Is it possible that greater post-operative recovery of the ventilatory function would take place if the "good" side were not encircled by a pressure binder?

No difficulty was encountered in getting the patients to attempt a maximum breathing capacity between thoracoplasty stages. The test was done thirteen days after each operative stage and by that time practically all of the post-operative pain had disappeared. The patients understood that if any further surgery was necessary its performance was dependent upon the result of the test. Therefore they almost always made a very good effort. If the maximum breathing capacity was lowered by chest pain, the test was not discounted because of the pain, since it is recognized that chest pain itself can produce dyspnea by limiting the motion of the ribs and the diaphragm. If the maximum breathing capacity was too low in such instances, further operation was deferred until the pain subsided and the ventilation improved satisfactorily. It was felt that the maximum breathing capacity between stages gave a true picture of the ventilatory function at those times and was a reliable indication of the ability of the patient to undergo further operation.

The ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  is useful in detecting the presence or absence of true dyspnea. Four persons were studied who complained of "occasional dyspnea" but whose X-ray and clinical findings did not show reason for this symptom. In each case the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  was definitely below 0.30. When the definition of dyspnea (consciousness of the necessity for increased ventilatory effort) was carefully explained to each of these people they admitted that the sensation, which they had been referring to as dyspnea, was really a sense of "oppression or heaviness in the chest." For instance one apprehensive, "breathless" man had a maximum breathing capacity of 147 liters per minute, with a walking ventilation of 17 liters per minute. His

$\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  ratio was only 0.12, whereas slight dyspnea did not appear, in our experience, until this ratio approached 0.35.

The maximum breathing capacity and walking ventilation were studied in a few patients with disease other than tuberculosis and in a few tuberculous patients for purposes other than the evaluation of the predicted or actual functional effects of therapeutic pulmonary collapse. These included a patient with extensive cystic disease of the lungs, 2 patients with asthma, a few with silico-tuberculosis, one patient before and after pneumonectomy, a woman while pregnant and after delivery, and a few patients on humid days. These are mentioned to point out other possible uses of ventilatory studies. Results were interesting and helpful but these cases are too few to allow any definite conclusions to be drawn at this time.

The walking ventilation is a functional test. When properly performed it is conditioned principally by the patient's metabolic needs while walking. Although a measurement of ventilation, it is closely related to the respiratory aspect



of pulmonary function. The walking ventilation test is not strenuous and does not disclose what the ventilatory status of the patient would be under more energetic circumstances. An arrested case of tuberculosis is not encouraged to be energetic, however, and the ability of such a patient at least to walk at a leisurely pace without marked dyspnea seems a satisfactory minimum requirement of successful therapy.

The fact that the walking ventilation remained relatively constant in a given individual permitted its use as a base-line for estimating that patient's ventilatory requirement. When the walking ventilation changed more than 4 liters after thoracoplasty the postoperative walking ventilation was always lower than the preoperative one. In these cases the preoperative walking ventilation may have been higher because of emotional reaction to an unfamiliar test. On the other hand, the postoperative walking ventilation may have been lower because the ventilatory aspect of pulmonary function was more efficient after successful collapse of the diseased lung.

The object of this paper is to present our limited experience with a simplified procedure for evaluating certain aspects of ventilatory function in pulmonary tuberculosis. It is not intended as an exhaustive study of the many changes of pulmonary function or even all of the ventilatory changes in relation to various types of therapy. Any practical study which determines only a few aspects of pulmonary function suffers in comparison to those complete investigations which are so necessary to establish the entire physiological background of pulmonary function in tuberculosis. Yet there is a need for simplified procedures to evaluate pulmonary function, and objectively to determine or predict pulmonary insufficiency, which can be used in the smaller sanatoria and hospitals or in the physician's office unequipped for more elaborate tests. Determination of the maximum breathing capacity (repeated at necessary intervals) and the walking ventilation, together with observation of ventilatory movements by fluoroscopy will, we believe, give a picture of the status of pulmonary function which is adequate for practical purposes in the majority of patients. This procedure has been of great practical value at Laurel Heights in our experience of the past two and one-half years. Special training on the part of the operator or patient is not necessary. The apparatus is not expensive and is relatively simple to operate.

Study of ventilatory function alone will not evaluate certain complications of functional importance such as emphysema or cardiocirculatory impairment. An emphysematous lung is an inefficient lung. Emphysema in the lung to be collapsed is not a problem, since compressing the emphysematous area may even tend to improve the overall ventilatory efficiency. Because emphysema is present more frequently on the side to be collapsed and less frequently and extensively on the "good" side, it is not often necessary to evaluate quantitatively its presence. Patients with serious respiratory or cardiocirculatory complications had better be observed at the larger clinics where more detailed physiological studies can be done.

It is our belief, supported by experience, that careful observation under the

fluoroscope of the motions of the ribs and diaphragms on the two sides is a rough but adequate means of estimating the relative proportion of the total ventilation contributed by each lung, provided that the maximum breathing capacity is sufficiently large to allow for a considerable factor of safety (70 liters per minute or more). In such cases differential bronchspirometric studies have not been deemed necessary and have not been done—and this has been the case in approximately three-fourths of our patients who were candidates for thoracoplasty. In cases nearer the border-line, as judged by the maximum breathing capacity, walking ventilation and fluoroscopy, differential bronchspirometry is extremely helpful and has been employed in our series. However, should apparatus for differential bronchspirometry not be available, we believe that many of even the border-line cases can safely undergo collapse therapy if tests of the maximum breathing capacity are repeated at intervals (for example, between stages of thoracoplasty) to control the degree of pulmonary collapse which the patient will tolerate.

#### SUMMARY

1. A simple test for the determination of the walking ventilation is described.
2. Whereas the maximum breathing capacity is altered by changes in pulmonary disease and frequently by collapse therapy, the walking ventilation was found to remain relatively constant in any given patient.

3. Correlation between the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  and the degree of dyspnea present when walking is shown. Severe dyspnea on walking occurred when the ratio  $\frac{\text{Walking ventilation}}{\text{Maximum breathing capacity}}$  exceeded 0.50.

4. Since the walking ventilation was found to remain constant, it was postulated that collapse therapy should not reduce the maximum breathing capacity below twice the value of the walking ventilation, if the patient was to avoid severe dyspnea when ambulatory.

5. Fluoroscopic examination and determination of the maximum breathing capacity and the walking ventilation were used to evaluate the ventilatory function of 26 patients before and after thoracoplasty. Results are presented.

6. This simple procedure (fluoroscopic examination and determination of the maximum breathing capacity and the walking ventilation) was of practical value in selecting cases suitable for thoracoplasty and in controlling the degree of collapse therapy in those patients undergoing operation.

7. This means of studying ventilatory function also was found useful for evaluating the presence or imminence of dyspnea in patients with tuberculosis receiving other types of therapy than thoracoplasty and in persons with conditions other than tuberculosis. Special training on the part of the operator or the patient is not necessary. The apparatus is inexpensive and is easy to operate.

8. Illustrative case reports are included.

## SUMARIO

1. Descríbese aquí una prueba esencial para la determinación de la aeración ambulante.

2. En tanto que la capacidad respiratoria máxima es alterada por las modificaciones de la enfermedad pulmonar y frecuentemente por la colapsoterapia, la aeración ambulante permanece relativamente constante en cualquier enfermo dado.

3. Muéstrase aquí la correlación entre la razón  $\frac{\text{Aeración ambulante}}{\text{Capacidad respiratoria máxima}}$  y la intensidad de la disnea presente mientras se camina. Sobrevino disnea intensa en la marcha cuando la razón excedía de 0.50.

4. Como la aeración ambulante permaneció constante, opínase que la colapsoterapia no debe mermar la capacidad respiratoria máxima a menos del doble de la cifra de la aeración ambulante, si el enfermo va a evitar una disnea intensa al caminar.

5. A fin de justipreciar la función ventiladora de 26 enfermos antes y después de la toracoplastia, utilizáronse en el examen la roentgenoscopia y la determinación de la capacidad respiratoria máxima y de la aeración ambulante. Preséntase aquí el resultado.

6. Ese sencillo procedimiento (el examen roentgenoscópico y la determinación de la capacidad respiratoria máxima y de la aeración ambulante) resultó de valor práctico para escoger casos apropiados para la toracoplastia y para graduar la colapsoterapia en los enfermos en vías de operación.

7. Este medio de estudiar la función ventiladora resultó igualmente útil para avaluar la presencia o inminencia de disnea en los tuberculosos que recibían otros tratamientos distintos de la toracoplastia y en enfermos que padecían de otros estados distintos de la tuberculosis. No se necesita para ello preparación especial de parte del cirujano o del enfermo, y el aparato es poco costoso y fácil de operar.

8. Preséntanse historias clínicas típicas.

The author is indebted to Dr. Andre Cournand, Dr. George Wright, Dr. Edward J. Lynch and Dr. Kirby S. Howlett, Jr. for their advice and interest in this work and to Dr. Lee Reid for doing the bronchspirometric determinations.

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# BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS<sup>1</sup>

## IV. A Geographical Adventure

### Part 1

B. A. DORMER, J. FRIEDLANDER AND F. J. WILES

"Why grass is green, or why our blood is red  
Are mysteries which none have reached unto.  
In this low form, poor soul, what wilt thou do?  
When wilt thou shake off this pedantry,  
Of being taught by sense and fantasy?  
Thou look'st through spectacles; small things seem great  
Below; but up into the watch-tower get,  
And see all things despoiled of fallacies."

JOHN DONNE

This paper attempts to describe the appearance of the bronchial system in pulmonary tuberculosis. One's concept of an individual case is made up of many things—what one has read in books, heard from others, how one interprets shadows on an X-ray film, how one correlates physical signs with other findings, one's knowledge of postmortem examinations of tissues, both macroscopic and microscopic.

How often is this concept right? One has always tried to fit the history, the physical signs and the X-ray findings together like pieces of a jig-saw puzzle and then imagine the diseased lung as a working organism.

It was in 1925 that the senior author commenced to do bronchograms in pulmonary tuberculosis and since that date has made more than 2,000 individual studies. It is a study which has been eagerly pursued for a while and then dropped for years, but during the last two years it has become so important that a bronchogram is done in nearly every case in this clinic.

We have called this paper a geographical adventure because we found ourselves at first in a strange land with very few of the familiar landmarks with which physical signs, conventional radiography, macroscopic and microscopic pathology had made us familiar.

We had to make our own charts and maps and had to learn to regard the tuberculous lung as a living thing, handicapped by assaults on its normal structure and eventually left a bizarre travesty of its former self. We saw more and more how tuberculosis is a disease which does its greatest harm to the bronchial system and that all stages, from the very earliest, are accompanied by great and irreparable damage to the bronchial tree.

We also realized that all pulmonary disease is intimately concerned with bronchial block and its sequelae and that the end-result of such a block in tuberculosis in no way differs from a similar block from any other cause.

What happens when part of a bronchial tree becomes blocked? The area of lung supplied by that conduit will collapse. If the atelectatic area is sterile

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bacteriologically, the result will probably be an area of fibrosis. If there are organisms present a pneumonitis will develop and, depending on the degree of inflammatory response, the result will be an abscess cavity or a bronchiectasis or both. It is difficult to describe in words the happenings when a person becomes infected with tuberculosis, but the following cases illustrate our conception of the geography of the lungs so afflicted.

Let us set down briefly what we have learned from bronchography:

- 1: That it is safe. We have never seen a case made worse by the instillation of lipiodol into the bronchi. It must be noted that no case sensitive to iodides or cocaine is explored in this manner.
- 2: That block of some portion of the bronchial tree is invariably present in every case of pulmonary tuberculosis unless the area beyond the block has already broken down into a cavity. Even when there is the earliest demonstrable X-ray lesion this block occurs, usually in the bronchioles.
- 3: As a result of the bronchial or bronchiolar block there occurs cavitation or bronchiectasis and ultimately a distortion of the bronchial tree due to fibrosis in the affected area.
- 4: Tuberculous bronchiectasis and cavitation therefore arise in exactly the same way as do nontuberculous bronchiectasis or a pulmonary abscess (1).

The following cases are considered:

- 1: Predominantly exudative disease and its nontuberculous counterpart.
- 2: Predominantly productive disease and its nontuberculous counterpart.
- 3: Cases which have elements of both productive and exudative disease.

In each case we discuss very briefly:

- (a) The history.
- (b) The physical findings.
- (c) The conventional radiogram.
- (d) The bronchogram.

It will be noted in each case that (a), (b) and (c) fail to give the true picture and it is only the bronchogram which gives us the additional information to form a picture of a living but damaged organism and to guide us in the possible lines of therapy to adopt for each case.

#### CASE REPORTS

##### *Group I. Cases with Predominantly Exudative Disease*

*Case 1:* E. 647, European male, aged thirty-three. He had a sudden onset of illness three months before bronchogram with acute pain on the right side of the chest followed by hemoptysis within a few hours. He lost 18 lbs. during the first six weeks of his illness although the pain subsided in a week. He has a cough and brings up a little sputum but does not feel ill. He is a fit looking man. Temperature is between 97 and 99.2°F.; pulse 80 to 90. Sputum contains tubercle bacilli. The only physical sign is increased vocal resonance over the right upper lobe.

X-ray films show a clouded apex and some scattered infiltration in the right infraclavicular region and midzone, especially towards the periphery.



FIG. 1. Upper left; FIG. 2. Upper right; FIG. 3. Lower left; FIG. 4. Lower centre; FIG. 5. Lower right

Bronchogram (figure 1) shows a normal bronchial tree in the extreme apex and the base, but in the area of infiltration the bronchi are blocked and the alveolar pattern fails to be revealed. This means atelectasis in the area beyond the block and accounts for the infiltration seen in the conventional radiograph. A bronchogram, taken a fortnight later, shows a similar picture, but one of the atelectatic areas has excavated and discharged into a bronchus.

We now have a living picture. This case which has probably been a primary inhalation infection has speedily spread from alveoli to lymph nodes. There has occurred a block of the bronchioles feeding this area from swelling of the bronchi due to allergy or from swelling of the lymph nodes and bulge block of the bronchioles. This is followed by small areas of atelectasis and the appearance of infiltration and later excavation of the atelectatic areas, leaving small cavities communicating with the bronchioles.

In this case the history suggests an acute infection, probably tuberculous, the physical signs point to a probable lesion in the right upper lobe. The conventional X-ray film shows an early infiltrative lesion in this area, and the bronchogram gives one the living picture..

*Case 2:* O. P., native male, aged twenty-three. He was working as a dock laborer until the day before admission. He had felt tired and "off" food for one month. For one week he had been short of breath and had pain in his chest. Cough is a minor feature and he has a little sputum. He is an ill looking native man but quite well nourished. Temperature is between 97 and 102°F., swinging septic type; pulse 120. Sputum contains tubercle bacilli. The physical signs are crepitations over the whole of the left lung and the right upper lobe.

Radiogram shows extensive primary progressive disease of the whole of the left lung and the right upper lobe. It was decided to study the right upper lobe which showed scattered infiltrations in the apex and infraclavicular regions.

A bronchogram (figure 2) of this side shows a normal bronchial system at the base, a lobar shrinking and cavitation with bronchiectasis of the right upper lobe.

The picture is now clearly revealed. There have been atelectatic areas in the right upper lobe due to bronchial block and the result has been shrinking of the lobe with excavation and bronchiectasis.

*Case 3:* C. 415, Indian male, aged twenty-seven. Three months ago he developed cough and pain on the left side of his chest. On admission his only complaint was cough and he had a little sputum. He is a fit looking Indian male. Temperature is between 99 and 99.8°F.; pulse 80 to 90. Sputum contains tubercle bacilli. The only physical signs are crepitations in the left infraclavicular region.

X-ray film (figure 3) shows clouding of the left apex. There are scattered areas of infiltration in the left infraclavicular region and midzone. There is an area of infiltration in the right midzone at the periphery.

A bronchogram (figure 4) shows blocking of the bronchioles in the left infraclavicular and midzones and three well marked cavities, one of which is a distorted and dilated bronchus. There is a slight but perceptible shift of the mediastinum to the left.

The picture is one of bronchiolar block leading to scattered areas of atelectasis. The resulting cavities and bronchiectasis have followed soon after the initial

block. This is an early case but the damage has been swiftly executed and the normal geographical features have been changed beyond recognition and the only true map is made by the aid of bronchography.

*Case 4:* O. P., native male, aged forty. Some months ago he began to have pain in the chest, hemoptysis, profuse night sweats, loss of weight and appetite. He is an ill looking man and his breath is foul. His temperature is up to 100°F. at night; pulse 120. Sputum is copious, offensive and persistently negative for tubercle bacilli. Blood Wassermann reaction is strongly positive. Physical signs are rhonchi all over the chest. Crepitations are present at the right apex and also on the left side below the scapular angle.

X-ray examination shows extensive infiltration in the right infraclavicular region and midzone and a similar infiltration at the left midzone and base.

A bronchogram (figure 5) shows excavation of the right upper lobe, a mixture of plain cavity and bronchiectasis. At the left base there is an advanced bronchiectasis.

There was no evidence of tuberculosis in this case, yet the picture revealed by bronchography is no different from that produced by tuberculosis. The basic changes appear to have been a block of the bronchi, leading in the right lung to cavitation and in the left to bronchiectasis.

The patient improved rapidly on anti-syphilitic treatment, but disappeared from the hospital when he felt well so we were unable to prove a syphilitic origin of his pulmonary lesions.

*Case 5:* C. 266, Indian male, aged twenty-six. He commenced coughing four months ago and lost a little weight. He continued working until a month before admission to the hospital, but then went to bed because of fever. The day after he went to bed he had a severe hemoptysis. He is a fit looking Indian. His temperature is between 99 and 99.8°F.; pulse 100 to 108. Sputum contains tubercle bacilli. The only physical signs are some crepitations over the upper lobes of both lungs.

X-ray film (figure 6) shows clouding of the right apex and infiltration throughout the right upper lobe. There is scattered infiltration throughout the rest of the right lung. The left lung shows scattered infiltration in the midzone and base.

A bronchographic study of the right lung (figure 7) was made and shows the right upper lobe to be the seat of a massive bronchiectatic excavation. The bronchial tree in the lower lobe is normal.

Physical signs and conventional radiography in this case, taken alone, would have given us a completely wrong impression. Bronchography alone gives us the true map of the disease and emphasizes the devastating effect of tuberculosis on the bronchi.

*Case 6:* C. 309, colored female, aged twenty-three. Two months ago she became ill fairly suddenly with fever, general malaise and weakness. She had a cough which was not troublesome and she brought up a little sputum. She is a well looking colored woman. Temperature is between 100 and 101°F.; pulse 110 to 120. Sputum contains tubercle bacilli. Physical signs are impaired air entry at the left upper lobe, back and front and crepitations over this area. There are a few crepitations over the upper lobe on the right.

An X-ray film (figure 8) shows extensive infiltration of the left apex and infraclavicular



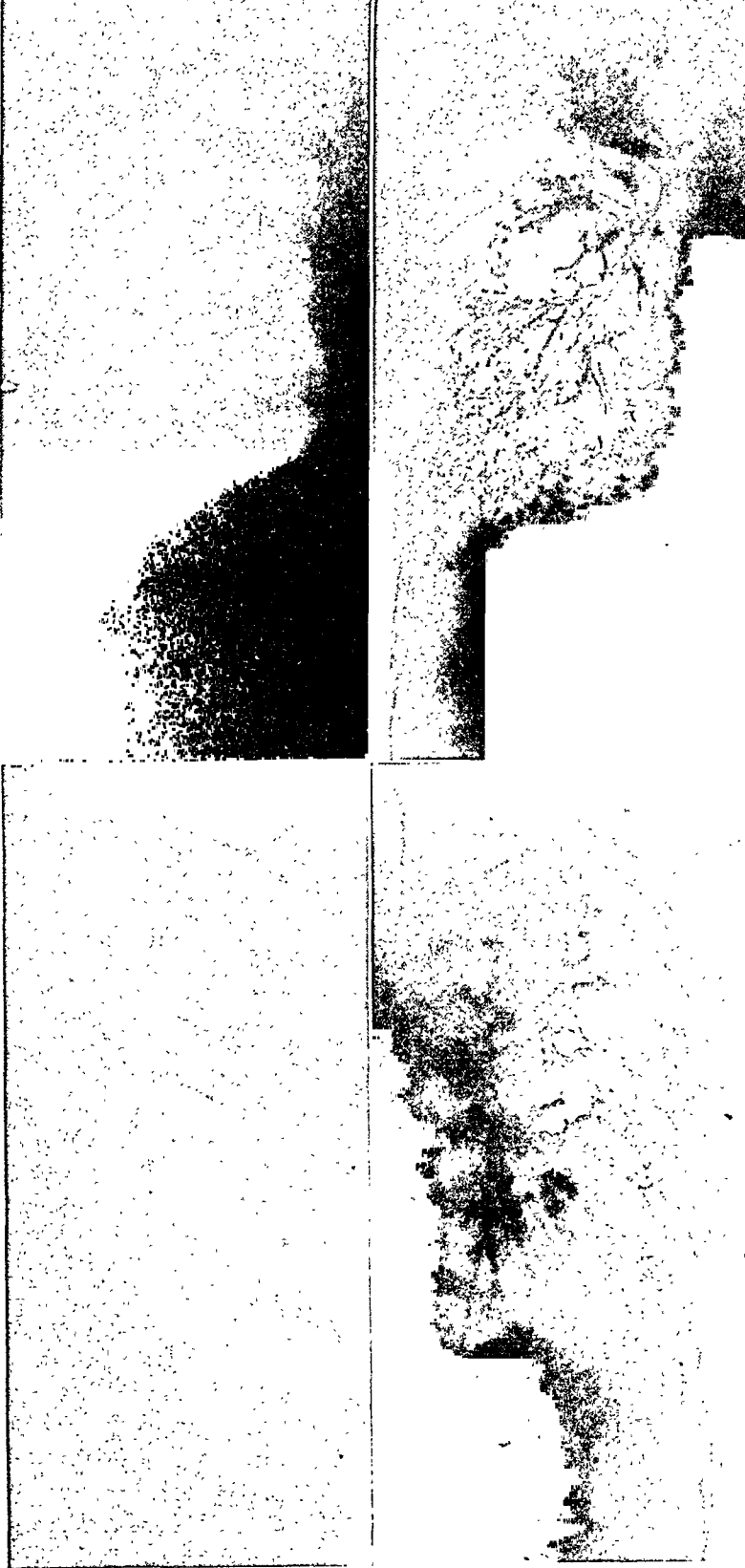


FIG. 6. Upper left; FIG. 7. Upper right; FIG. 8. Lower left; FIG. 9. Lower right.



FIG. 10. Upper left; FIG. 11. Upper right; FIG. 12. Lower.

region; scattered infiltration throughout the rest of the left lung. The right side shows scattered infiltration throughout.

A bronchogram of the left lung (figure 9) shows extensive cavitation and bronchiectasis of the left upper lobe and blocking of bronchioles in other areas of infiltration with occasional small cavities.

*Case 7:* O. P., native male, aged twenty-seven. He gives a history of six weeks' illness only. He was working as a laborer and began to feel tired, had fever and lack of appetite. He was admitted to the hospital as a case of enteric fever. He is an ill looking native male but not thin. Temperature is 102°F.; pulse 140. He is dyspneic. Sputum contains tubercle bacilli. Clinical examination reveals no abnormal physical signs indicative of pulmonary disease.

Roentgenogram (figure 10) shows confluent miliary tuberculosis.

A bronchogram of the right side (figure 11) shows there is no alveolar filling—the bronchial map terminates at the bronchioles. At the apex the bronchi are dilated. One bronchus at the base terminates in a cavity.

It must be emphasized that the failure of lipiodol to reach the alveoli is not a question of technique, but that the bronchioles are really blocked.

This case shows that, even in a rapidly developing lethal type of miliary tuberculosis, the bronchioles are blocked and that there is time for terminal excavation. One of the reasons for rapid death is asphyxia, because the air cannot get to the alveoli and oxygen exchange is thereby prevented.

*Case 8:* C. 414, colored male, aged twenty-seven. His onset was four months ago with hemoptysis. He coughed up two pints of blood in twenty-four hours. Now he has cough and sputum. He is a fit looking colored man. His temperature and pulse are normal. Sputum contains tubercle bacilli. Physical signs are crepitations throughout the right lung.

A roentgenogram shows extensive infiltration throughout the right lung.

A bronchogram shows that lipiodol fails to enter the alveoli; the block is in the bronchioles. Another bronchogram (figure 12), done six weeks later, shows much the same picture, but bronchiectasis is developing in the midzone bronchi. A tapering block of extreme apical bronchus is seen as it was in the first bronchogram.

In order to demonstrate that the bronchiolar block was not due to faulty technique, another bronchogram was done six weeks after the first—after all the previous lipiodol had disappeared. The only difference was the expected appearance of areas of bronchiectasis.

*Part 2 will appear in the next issue*

# DIASONE THERAPY OF PULMONARY TUBERCULOSIS<sup>1</sup>

Its Clinical Efficacy and Toxicity

LOUIS BENSON<sup>2</sup> AND LOUIS GOODMAN<sup>3</sup>

With the technical assistance of Corinne Manuel

The recent regrettable publicity given to diasone therapy of tuberculosis in the lay press, as well as the publication of the *Report of the Committee on Therapy* of the American Trudeau Society (1), prompts us to record our experience with this agent in the treatment of a small series of patients with pulmonary tuberculosis.

## MATERIAL AND METHODS

Twenty-two patients with pulmonary tuberculosis were selected for study, 11 males and 11 females. The ages varied from 17 to 46 years. All were hospitalized at the State of Vermont Sanatorium for Tuberculosis. Various types and stages of pulmonary tuberculosis were included, but only cases were selected in which the course of the disease had been carefully followed for many months and in which the pulmonary lesions were found to be sufficiently static to permit appraisal of the effects of long-term medication with diasone. The disease was bilateral in 18 patients. Nine patients showed far advanced pulmonary tuberculosis and 12 moderately advanced pulmonary tuberculosis. The majority had cavitation. Thirteen patients had artificial pneumothorax which was bilateral in 3. A positive sputum was present in all but one patient. The duration of the disease varied from a few months to more than eighteen years, being longer than two years in all but 4 cases. Five patients were on absolute bed-rest. Nearly all showed a slowly progressive disease process.

Diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) was administered orally in capsules.<sup>4</sup> The dose was usually 0.33 g., three times daily with meals. Occasionally medication had to be temporarily omitted or reduced in amount because of toxic side-effects.

The patients were seen at least twice daily by one of us (L. B.). Clinical and laboratory indices routinely followed and recorded included body temperature (twice daily); body weight (once weekly); chest roentgenograms (semi-monthly); twenty-four-hour sputum volume (weekly); complete sputum examination (weekly) including concentration, culture, guinea pig inoculation and Gaffky count, as indicated; examination and culture of aspirated gastric contents as

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<sup>4</sup> Supplied by the Abbott Laboratories, North Chicago, Illinois, through the courtesy of Dr. Richard K. Richards, Chief Pharmacologist. Each capsule contained 0.33 g. diasone, with 10 per cent of sodium bicarbonate added.

indicated; complete urinalysis, erythrocyte sedimentation rate and complete blood count (semi-monthly); and periodic determination of blood levels of free diasone. In addition, urinary diasone determinations were done at least once on each patient. The level of drug in the pleural exudate of patients with pleural effusion was also determined. Diasone was determined colorimetrically by a modification of the sulfonamide method of Bratton and Marshall (2), employing freshly made dilutions of diasone as standards. In an occasional patient showing more than the usual cyanosis which occurs in diasone therapy, the blood was examined spectroscopically for methemoglobin and sulfhemoglobin.

### RESULTS

All patients except 3 were on diasone medication for 120 to 160 days. Of these 3 patients, 2 died while on treatment and one had an exfoliative dermatitis necessitating discontinuance of diasone. To date the series has been followed

TABLE 1

*Clinical results with diasone therapy of pulmonary tuberculosis in 22 patients*

	EXTENT OF DISEASE			Total
	Far advanced	Moderately advanced	Minimal	
No Change.....	5	2	1	8
Improved.....	1	6		7
Worse.....	2	3		5
Died.....	1	1		2
Total.....	9	12	1	22

for an additional three months posttherapy period, making the total time of observation seven months. As a result of careful analysis of the clinical, laboratory and roentgenographic indices enumerated above, the results obtained can be tabulated as shown in table 1.

Further analysis of the 7 cases in which some improvement was manifested revealed that in no single instance was it possible unequivocally to attribute the improvement to diasone therapy. In other words, such changes for the better as did occur are routinely seen in a comparable group of hospitalized patients with pulmonary tuberculosis not receiving specific chemotherapy. An analysis of results on the basis of major clinical indices and laboratory findings appears in table 2. In this table, the term "no significant change" is used to indicate that the enumerated clinical and laboratory findings did not vary in their range or order of magnitude during the period of therapy from those findings previously recorded during the control period.

It is possible, however, that in 4 patients diasone therapy may have played a part in the improvement seen. If this be granted, then the percentage of patients obtaining benefit from diasone is at best only 18 per cent, a figure considerably below the 93 per cent reported by Petter and Prenzlau (3, 4). Inspec-

tion of table 2 also reveals that in a number of patients the volume of sputum and number of tubercle bacilli in the sputum were definitely decreased. The significance and explanation of this observation are not clear. There was no positive correlation discernible between this finding and improvement in the clinical status of the patient. Of the 21 patients with positive sputa, reversal to a negative sputum<sup>5</sup> occurred in only 4 while on diasone. This figure is far below that reported by Petter and Prenzlau who observed a reversal of sputum from positive to negative in 59 per cent of 44 cases.

A comparison of the clinical course of patients during the four-month period of diasone medication with that of the subsequent three-month postdiasone period failed to indicate any significant change or any late therapeutic benefit. In other words, those who improved maintained their improvement as a rule,

TABLE 2  
*Effects of diasone therapy on clinical and laboratory findings*

	NUMBER OF PATIENTS			
	No significant change	Improvement	Worse	Total
Body temperature.....	14	3	5	22
Body weight.....	12	4	6	22
Sedimentation rate.....	16	3	3	22
Sputum volume.....	9	10	3	22
Gaffky count.....	12	10	0	22
Chest roentgenogram.....	10	4	8	22

and those who had shown no change or who were worse did not show any delayed beneficial effect.

#### TOXICITY

Diasone is not an innocuous drug and a variety of toxic and untoward responses were observed in this study. All but 3 patients exhibited one or more toxic effects. Cyanosis was observed in more than one-half of the patients. It usually appeared within several days after diasone medication was initiated and persisted so long as therapy was continued. Its intensity bore no relation to the blood level of diasone. Spectroscopic examination of the blood in several patients showing marked cyanosis failed to reveal methemoglobin or sulfhemoglobin. (The method employed was capable of detecting approximately 0.5 g. per cent methemoglobin.) Fatigue was observed in 12 patients and disappeared when diasone was withdrawn. Headache was complained of by 9 patients and in one case it was so intense that a diagnostic lumbar puncture was performed. Dyspnea, unexplainable on the basis either of anemia or of the pulmonary status

<sup>5</sup> The term "negative sputum" as used in this report signifies that at monthly intervals for three consecutive months the sputum was found to be negative on direct smear, after concentration of a three-day specimen, on culture, and on guinea pig inoculation.

of the patient, occurred in 6 cases. In 3 patients dyspnea was associated with cyanosis. It tended to occur early in the course of diasone therapy and disappeared despite continuance of medication. *Nervousness* and *vertigo* were frequent complaints in approximately one-quarter of the patients. Other untoward effects observed were *anorexia*, *nausea*, *epigastric distress*, *diarrhea*, *disorientation*, *restlessness*, *insomnia*, *tremors*, *diplopia*, *myalgia*, *palpitation*, *tachycardia*, *jaundice*, *pallor*, *fever*, *thyroid enlargement* and *dermatitis*. An exfoliative dermatitis occurred in one patient as follows:

*Exfoliative dermatitis due to diasone:* A. A., age 35, white male, painter by trade, entered the Sanatorium in July, 1941. He had far advanced pulmonary tuberculosis, with mixed infiltration and cavitation, well localized. The lesions were unstable and slowly progressive. The clinical status was active and unimproved. The patient received bilateral pneumothorax 1941-1942. He was on modified bed-rest when diasone was started November 10, 1943 at the dose level of 0.33 g., three times a day. On November 15, headache developed; on the 16th myalgia and weakness were noted; and on the 18th cyanosis accompanied by dyspnea, and anorexia associated with nausea were added to the picture. On this day there also was noted a generalized macular rash which grew in intensity. The various symptoms noted above persisted for from six to fourteen days and then subsided, except that the skin lesions persisted and began exfoliating on December 3, at which time the diasone was discontinued. The exfoliation continued until December 10. On December 14, a single 0.33 g. dose of diasone was again given. The dermatitis recurred within twenty-four hours, exfoliated within two days and persisted for ten days. No further attempt at diasone therapy was made.

In another patient, not included in this series, a severe exfoliative dermatitis with high fever developed after two weeks of diasone therapy and necessitated cessation of medication.

One patient, a 17-year-old girl, gradually developed moderate symmetrical enlargement of the thyroid gland under diasone therapy. Signs and symptoms of thyroid dysfunction were absent. Other effects of diasone noted in this patient were fatigue, headache, dyspnea and cyanosis. The patient's pulmonary condition was unaffected by diasone. The thyroid enlargement has persisted for three months after discontinuation of the drug.

A consistent toxic effect of diasone seen in nearly every patient was the occurrence of anemia. It was usually mild and hypochromic in character. In 5 cases, however, the anemia was of moderate intensity, the hemoglobin and red blood cell count falling 30 to 40 per cent below their pre-diasone values. The anemia bore no clear relation to the occurrence of cyanosis or to the level of diasone in the blood. It persisted throughout the period of diasone medication, after which the blood values slowly returned to normal. No evidence of leucopenia or neutropenia was observed.

Renal function did not appear to be impaired, nor was there evidence of dysfunction of the urinary tract. Repeated chemical and microscopical examination of the urine indicated nothing abnormal, except that several patients at some time showed in their urine a substance capable of reducing Benedict's solution to a slight degree. It is likely that this reduction is due to the urinary excretion

of some degradation product of diasone, inasmuch as diasone itself when added to urine does not cause reduction.

#### DEATHS

Two patients died while on diasone therapy. Unfortunately, permission for postmortem examinations was not obtained. From the data available, it is impossible to decide whether diasone occupied a possible etiological rôle in the fatal outcome. Brief summaries of the 2 fatal cases follow.

*H. M.*, age 46, a white male, woolen-mill spinner, entered the Sanatorium in December, 1937 with moderately advanced bilateral pulmonary tuberculosis and with extensive cavitation in the right lung. The lesions were unstable and slowly progressive. At the time that diasone was started on November 8, 1943, at the dose level of 0.33 g. three times daily, the clinical status was active and unimproved and the patient was on modified bed-rest. A variety of toxic effects were observed, particularly during the first few weeks of medication. These included dizziness, fatigue, pallor, nervousness, palpitation, dyspnea and cyanosis. On December 1, the patient's temperature began to rise and remained between 100° and 101°F. throughout the period of diasone medication. Dyspnea gradually became more marked. Breathing was asthmatic in character, and epinephrine gave no relief. On April 12, 1944, the 154th day of diasone therapy, the patient had several episodes of severe paroxysmal dyspnea associated with acute pulmonary edema and died. Physical examination and roentgenographic examination of the chest on the day prior to death were negative for cardiac disease. Permission for autopsy was not obtained.

*R. L.*, age 23, white female, housewife, reentered the Sanatorium in January, 1943 with far advanced bilateral pulmonary tuberculosis of six years' duration. There was mixed infiltration with cavitation scattered throughout both lungs. The lesions were unstable and rapidly progressive. The clinical status was active and unimproved. The patient was on absolute bed-rest when diasone therapy, 0.33 g. three times daily, was started, on November 8. Fatigue was marked between November 16 and 30. A moderate degree of anemia developed, which became more severe by February, 1944 (red cells 2,060,000; hemoglobin 7.0 g. per cent). On February 2, 1944, the 86th day of therapy, the patient had a sudden profuse pulmonary hemorrhage and died within three minutes. Permission for a postmortem examination was not obtained.

#### DIASONE LEVELS IN BODY FLUIDS

Blood levels of diasone varied considerably from patient to patient and also from time to time in the same patient. In general, however, the blood levels obtained were of the order of magnitude that one might predict from assuming (1) fairly complete intestinal absorption, (2) renal excretion sufficiently adequate to prevent cumulation of the drug in the body, and (3) distribution of the drug throughout the total body water. Thus, blood levels of free diasone ranging from 0.2 to 3.2 mg. per cent were observed. Approximately 80 per cent of all the determinations fell between 0.5 and 2.0 mg. per cent. No predictable correlation was observed between the level of diasone in the blood and the nature or severity of toxic responses. Also, there was no detectable relationship



between blood diasone levels and therapeutic response. Diasone was found in the pleural exudates of patients with pleural effusion. In general, the level in the pleural fluid tended to be slightly lower than that of the simultaneously determined blood. In one instance, tubercle bacilli were cultured from the pleural fluid which contained 2.8 mg. per cent free diasone. Concentration of the drug in the urine varied from 7 to 34 mg. per cent for free diasone, and from 15 to 42 mg. per cent for total diasone. Approximately 15 to 20 per cent of the urinary diasone was conjugated, the range being from 6 to 55 per cent.

#### DISCUSSION

Although the sulfonamides have not proved to be tuberculotherapeutic agents, compounds of the "sulfone" group appear to offer some promise, particularly 4,4'-diaminodiphenylsulfone and its derivatives. Among the latter, the three which have been studied at some length are promin (sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate), diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) and promizole (4,2'-diaminodiphenyl-5'-thiazolesulfone). The parent compound, 4,4'-diaminodiphenylsulfone, has been found to inhibit experimental tuberculosis in guinea pigs (5, 6, 7). Promin has likewise been shown to exert a salutary effect in experimental tuberculosis in guinea pigs (8, 9, 10). In addition, promin has been reported to exert a favorable effect in human tuberculosis when given orally (11, 12) but not when administered intravenously (13). Promizole also exerts a tuberculotherapeutic action in experimentally infected guinea pigs (14) and is currently being tried clinically in tuberculosis (15, 16).

Diasone was simultaneously and independently synthesized and described by Raiziss and his associates (17) and by Bauer and Rosenthal (18). Its chemical and physical properties have been reviewed in detail by Raiziss and associates (17). The compound was originally studied for its therapeutic value in experimental streptococcal and pneumococcal infections in mice, but was later shown to exert a beneficial effect in experimental tuberculosis in guinea pigs (19, 20). Petter (3) and Petter and Prenzlau (4) have recently reported very favorable clinical results with the use of diasone in the treatment of tuberculosis.

The many difficulties inherent in the clinical assay of drugs employed in the chemotherapy of human tuberculosis have been pointed out by almost every worker in the field and need not be enumerated here. In our series of 22 patients, we were unable to detect unequivocal evidence that diasone is a valuable chemotherapeutic agent in pulmonary tuberculosis. Only 7 patients showed improvement while on diasone therapy. Of these 7, only 4 could be considered as manifesting drug-induced improvement. Each of the 4 had moderately advanced disease and each manifested reversal of the sputum from positive to negative. It is possible that little benefit can be expected in patients with far advanced pulmonary tuberculosis and extensive tissue destruction. At best, only 18 per cent of our series derived benefit from diasone, and the possibility still exists that none of the 7 patients exhibited specific salutary effects from the drug. Our experience, while limited, is in contrast to the results of Petter and

Prenzlau (4) who reported improvement in 93 per cent of 44 patients treated with diasone for four months.

The length of treatment employed by us was such as to permit detection of improvement in pulmonary tuberculosis from the employment of chemotherapeutic agents, inasmuch as it is usually considered that from 120 to 150 days of medication are sufficient for a preliminary assay in properly selected patients. The daily dose of diasone was at the upper limit of tolerance, as indicated by the facts that a number of patients required temporary reduction in the amount prescribed and that nearly all patients exhibited one or more toxic effects. Analysis of the major clinical and laboratory indices (see table 2) fails to indicate significant benefit from diasone, except that in a number of patients there was an appreciable reduction of the amount of sputum and a temporary disappearance of tubercle bacilli from the sputum. The importance of this observation remains to be elucidated. Petter and Prenzlau also report reversal of the sputum from positive to negative, but the percentage of patients in their series showing this reversal is considerably in excess of that recorded here.

With regard to the toxicity of diasone, most patients experienced a variety of subjective complaints such as headache, nausea, anorexia, myalgia, dizziness, dyspnea, fatigue, palpitation, nervousness, etc. Objective evidence of toxicity revealed itself in cyanosis, fever, dermatitis, jaundice, tremors and anemia. Diasone can cause an exfoliative dermatitis. We have seen 2 such cases, and Pfuetze and Pyle (21) have recently recorded a case. The occurrence of thyroid enlargement in one patient may represent an anti-thyroid, goitrogenic action of diasone similar to that manifested by certain sulfonamides and by thiourea and its derivatives, particularly thiouracil. In this connection, Feldman and co-workers (14) reported that promizole administered to guinea pigs causes a diffuse parenchymatous hyperplasia of the thyroid and a loss of colloid. Similar effects of promizole were observed in rats by Higgins and Larson (22). The propensity for diasone to cause anemia is shared by most derivatives of diaminodiphenyl-sulfone (4, 7, 11, 14, 20, 23). Clinically, the anemia may be moderately severe, as was true in some of the cases reported here. Although reversible, this feature of diasone therapy may represent a handicap to its usefulness. Certainly, frequent examinations should be made of the blood of all patients receiving the drug. There was no evidence of a toxic action of diasone on white blood cells. However, other sulfones may cause agranulocytosis (12). The mechanism of the cyanosis caused by diasone is not clear. It may be due to a colored oxidation product of diasone, although methemoglobinemia has not been ruled out conclusively. As in the case of cyanosis due to sulfanilamide, considerable investigation may be required to elucidate the cause (for details, see discussion by Goodman and Gilman (24)).

Blood and urine diasone levels cannot be used as a safe guide to medication. The tolerance of the patient for the drug is the best index. The dose of 0.33 g. three times daily should rarely be exceeded. It has not been possible to correlate blood diasone levels either with toxic responses or with therapeutic effects. Despite a fairly high concentration of diasone in the pleural fluid, tubercle bacilli

were still present in the pleural exudate of one of our patients. Apparently the sulfones are not highly bactericidal as employed clinically, for a somewhat similar experience is recorded by Hinshaw and associates (12). In their patient, promin was instilled into an open empyema cavity almost daily for more than one year, yet tubercle bacilli were still present in the pus, although their number was considerably reduced.

It should be emphasized that diasone is an experimental drug which is not available for general distribution and should be employed only when careful clinical supervision and adequate laboratory facilities are available. On the basis of our limited experience with the drug, which has not been very promising, we are in complete accord with the cautious view adopted by the Committee on Therapy of the American Trudeau Society (1). A final appraisal of the value of diasone must await an analysis of results obtained with it in a large number of patients. Meanwhile, the search must continue for more effective and less toxic tuberculotherapeutic compounds.

#### SUMMARY

1. Diasone was administered for from 120 to 160 days to 22 patients with pulmonary tuberculosis. Analysis of pertinent data indicates that only 4 patients may possibly have benefited from the drug.

2. Two patients in the series died while on diasone therapy. Another patient developed an exfoliative dermatitis necessitating withdrawal of diasone. A second case of exfoliative dermatitis occurred but is not included in this series. A variety of toxic and untoward responses to diasone have been observed, including cyanosis, anemia, dermatitis, fever, jaundice, tremors, diplopia and enlargement of the thyroid.

3. Diasone is an experimental drug which is currently being investigated in several clinics for its tuberculotherapeutic value. It should be employed only under the most rigid clinical and laboratory control. A cautious attitude is necessary toward its ultimate value in the treatment of human tuberculosis.

#### SUMARIO

1. A 22 enfermos con tuberculosis pulmonar se les administró diasona por espacio de ciento veinte a ciento sesenta días. El análisis de datos pertinentes indica que sólo cuatro enfermos habían podido beneficiarse de la droga.

2. Dos enfermos de la serie fallecieron mientras recibían la diasona y otro manifestó una dermatitis exfoliativa que impuso la supresión de la droga. Se presentó otro caso de dermatitis exfoliativa, pero no figura en esta serie. Se han observado varias respuestas tóxicas o contraproducentes a la diasona, incluso cianosis, anemia, dermatitis, fiebre, ictericia, temblores, diplopía e hipertrofia tiroidea.

3. La diasona es una droga experimental que se está investigando hoy día en varias clínicas en cuanto a su valor tuberculoterapéutico y que sólo debe ser empleada bajo la más rígida fiscalización clínica y de laboratorio, de manera que

se impone la cautela al juzgar su valor definitivo en el tratamiento de la tuberculosis humana.

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# FATAL PEMPHIGOID REACTION TO DIASONE<sup>1,2</sup>

EDWARD H. ROBITZEK

The introduction of therapeutic agents into the medical armamentarium is frequently hazardous. Although the factors of safety are exhaustively studied by animal experimentation, individual idiosyncratic sensitivity often cannot be predicted. Unfortunate experiences with some of the earlier sulfone derivatives dictated special precaution in the determinations of the toxicity of diasone (disodium formaldehyde sulfoxylate derivative of diaminodiphenylsulfone). Such precautions were observed in the studies undertaken by Callomon (1) and also by Feldman, Hinshaw and Moses (2). Similar studies were made by Smith, Emmart and Stohlman (3). All authors agreed that there were wide margins of safety in experimental animals. Reports on the application of diasone to humans have, to date, been few, but the numbers are increasing. A general nonstatistical concensus appears to suggest that the same wide range of safety obtains for humans that has been noted in animals.

Petter and Prenzlau (4) have reported 44 patients who have undergone treatment for more than 120 days and have referred briefly to an additional 21 who have been under treatment for 60 or more days. They have recorded a fairly comprehensive range of toxic manifestations, all of which, however, were relatively mild and none of which were irreversible. They tended to clear up completely at the conclusion of three to four weeks when drug tolerance was established. It is not within the province of this report to discuss all of these reactions nor to report our own experiences. At this time we are solely concerned with skin lesions. Petter and Prenzlau include in their series one case of drug dermatitis. It cleared on temporary discontinuation of the drug and failed to reappear despite resumption and increase to 0.66 g. per day.

Another cutaneous reaction which presented certain features remarkably similar to our own was reported by Pfuete and Pyle (5). Their patient developed a generalized exfoliative dermatitis accompanied by a systemic reaction of considerable severity. Recovery from the skin lesion was complete.

The purpose of this report is to present a case of dermatitis which was fatal.

## CASE REPORT

R. P., a 17 year old colored female, had the onset of typical symptoms of pulmonary tuberculosis in February, 1941. She was admitted to Sea View Hospital in April, 1941 with a right pneumothorax which was obviously ineffectual and, in consequence, quickly abandoned. All other forms of therapy were steadfastly refused by the patient until April 3, 1944 when, after a thorough preliminary workup, she was brought to the diasone conference. She had a moderate anemia (hemoglobin 72 per cent; red blood cells 3,760,000) and a strongly positive sputum (Gaffky VIII) but there was no evidence of

<sup>1</sup> From the Medical Service of Dr. George G. Ornstein, Medical Director, Sea View Hospital, Staten Island, New York.

<sup>2</sup> Abbott Laboratories, through the courtesy of Dr. George Hazel, supplied the diasone used in this study.

extrapulmonary disease. She was accepted for therapy with the classification "very far advanced." This was in accordance with the policy of the conference of accepting for its diasone study patients who represented a cross section of the various phases of tuberculous pulmonary disease.

The initial dose of one-third gram of diasone was given on April 12, 1944. Five days later, April 17, the dose was increased to two-thirds gram per day and one week later, April 25, there being neither subjective nor objective evidence of toxicity, the full dose of 1 g. per day was begun. The method of administration was one capsule (one-third gram) with each meal. Weekly diasone blood levels gradually rose from a "trace" to 3 mg. per cent on May 2, 1944, one week after the full dose had been established.

On the twenty-sixth day following administration of the first dose (May 8, 1944), the patient began to complain of swelling of the lips. Examination revealed small herpetiform lesions. The temperature was 100° F. The blood count showed 45 per cent hemoglobin (7.5 g.); 2,400,000 red cells; 12,400 white cells; 66 per cent segmented, 14 per cent nonsegmented polynuclear leucocytes, 17 per cent lymphocytes; 3 per cent mononuclear cells; achromasia, polychromasia and stippling. The diasone was cut to two capsules (two-thirds gram) per day, the dose at breakfast being omitted.

On the following day, May 9, 1944, the urine showed a very faint trace of albumin, an occasional white cell, acid reaction and a specific gravity of 1.010. The sputum was Gaffky VIII. The blood diasone level was 0.9 mg. per cent and the sedimentation rate was 75 mm. in one hour. The patient felt well but the swelling and soreness about the lips persisted and the temperature which had remained about 100° F. all day rose by evening to 103° F.

On May 10, 1944 the patient began to experience chills and malaise and the temperature rose to 104° F. There had been progression of the labial lesions to the anterior portion of the tongue. In addition, small maculopapular, reddish lesions were now present over the anterior chest, palms and soles of the feet. In the latter areas they were moderately pruritic. The breath was fetid. There was unquestionable secondary mouth infection and, although the diasone was felt to be responsible for the initial lesions, the rôle of this superimposed infection in the production of fever was still undetermined. Treatment consisted of discontinuation of the drug, gentian violet for the mucous membrane lesions, alkalis in moderate doses and intravenous infusions of 5 per cent dextrose in physiological saline. The urine contained a trace of albumin, 20 to 25 epithelial cells, clumps of white cells, 6 to 8 red cells per field and occasional trichomonas and bacteria. The reaction was acid, the specific gravity 1.025. The acetone test was negative. There were no diasone crystals.

On May 11, 1944 her condition had deteriorated and she was given a transfusion of 600 cc. of citrated blood by the indirect method. A blood count following the transfusion revealed a hemoglobin of 75 per cent (12.5 g.), 3,840,000 red cells, 12,300 white cells, 71 per cent segmented and 7 per cent nonsegmented polynuclear leucocytes, 21 per cent lymphocytes, 1 per cent eosinophils and a one-plus achromasia. The blood studies revealed sugar 140 mg. per cent and urea nitrogen 13 mg. per cent. The diasone blood level was 0.8 mg. per cent and the sedimentation rate was 97 mm. in one hour.

On May 12, 1944, four days after the onset of the skin lesions, the patient began to experience considerable difficulty in swallowing so that the infusions of 5 per cent dextrose in physiological saline constituted the major source of sustenance. The urine on this date continued to show a trace of albumin, 20 to 25 epithelial cells, 6 to 9 red cells, clumps of white cells, specific gravity of 1.025, acid reaction and an occasional trichomonas. A modified Marshal test on the urine still showed the presence of diasone.

On May 13, 1944 the rash, which was now indurated and had a dark red color, had spread over the hands, arms, trunk, legs and feet as well as over the mucous membranes of the nose, mouth and vagina. There were no petechiae. The spleen was not palpable and reëxamination of the lungs indicated an increase in the physical signs bilaterally. The exact nature of the underlying disease was difficult to evaluate on account of large amounts of intrabronchial mucus.

The skin lesion continued to progress and by May 14, 1944 it was present over the entire body without specific predilection. It had become pemphigoid in character. There were cherry sized vesicles and bullae (figure 1), the contents of which were clear in some areas and hemorrhagic in others. The dermatologists were now able to demonstrate a positive Nikolsky sign. Ten cc. of calcium gluconate (1.375 g.) were given



FIG. 1. Demonstrates the bullous nature of the lesions over the trunk and arm

intravenously and this dose was repeated six hours later. The secretions from the mucous membranes became progressively thicker and more difficult to remove. Breathing was labored and oxygen had to be administered. Adrenalin was also given in an attempt to dilate the bronchi and thus to provide better aeration.

On the following day, May 15, 1944, the urea nitrogen was still 11 mg. per cent. The urine contained a "very faint trace" of albumin and a "very faint trace" of sugar (continuous intravenous dextrose in saline during this period) and the diasone blood level was 0.15 mg. per cent. The sedimentation rate was 32 mm. in one hour and a blood culture which had been taken on May 14, 1944 was reported as showing no growth. Subsequent observations of this culture were confirmatory. The lesions continued to progress but the major difficulty was the maintenance of clear air passages since it was apparent that the exfoliations extended throughout the bronchial tree into the smallest radicals. Bronchial aspiration was not satisfactory and bronchoscopy seemed ill-advised. Despite



supportive measures the patient expired on the morning of May 16, 1944. The probable immediate cause of death was bronchopneumonia and asphyxia.

Autopsy permission was not obtained. A postmortem X-ray film demonstrated an extensive exudative process throughout the greater portion of the right lung and a huge excavation with an extensive exudative dissemination throughout the remainder of the left lung.

#### COMMENT

Toxic erythemata and pemphigoid lesions have been reported following the administration of many different drugs. Severe reactions (6) and even fatalities are not uncommon. It is apparently impossible to predict which patient will respond with such a reaction. The prognosis, once the lesions have appeared, seems to depend upon the individual's degree of sensitivity and the rapidity of drug destruction or excretion. In our case the latter occurred slowly since we were still able to recover 0.15 mg. per cent of diasone from the blood five days after its discontinuation. Its presence was maintained despite large amounts of fluid given intravenously and good renal function. It is interesting to speculate on the probable concentrations of the drug in the various organs and skin at the time of death. Unfortunately we were not prepared to make such determinations at that time. Furthermore, it is important to note that sensitivity did not develop until twenty-six days after the initial dose of diasone was given.

#### SUMMARY AND CONCLUSIONS

1. A patient is presented in whom a fatal reaction occurred during the course of diasone therapy.
2. Individual idiosyncracies to drugs inevitably appear. We cannot allow a report of "low toxicity" to take us off guard.
3. Skin lesions occurring in the course of diasone therapy are potentially serious and warrant stoppage of the drug.

#### SUMARIO Y CONCLUSIONES

1. Descríbese a un enfermo en el que sobrevino una reacción letal mientras recibía una serie de diasona.
2. Las idiosincrasias individuales a las drogas son inevitables y una declaración de "poca toxicidad" no debe hacer descuidar las precauciones habituales.
3. Las lesiones cutáneas que sobrevienen durante la diasonoterapia son potencialmente graves y justifican la suspensión inmediata de la droga.

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## TUBERCULIN TESTING OF MEDICAL STUDENTS<sup>1</sup>

The Reaction to Tuberculin of Second Year Medical Students at the College of Physicians and Surgeons, Columbia University

M. M. STEINBACH AND C. J. DUCA

For the past twenty years it has been the custom of this Department to perform tuberculin tests on second year medical students who volunteered for the test. Since 1936 careful records of these tests have been preserved. The work has always been done by a small group of students working under the authors' directions.

The results reported are all based on Mantoux tests. Old Tuberculin was obtained from the Board of Health, City of New York. Since the introduction of PPD, half of the students were tested with this type of tuberculin. There has never been any significant difference in the results obtained by the use of these two preparations, except under the conditions described below.

The medical students of this institution are carefully examined when they enter school, including X-ray examination of the chest, so that any individuals with active disease are eliminated at the time of admission.

The students were tested first with 0.001 mg. OT; those who did not react were retested a week later, with 0.01 mg. The maximum amount used was 0.1 mg., since persons not reacting to this dose were, in our experience, almost always negative to 1.0 mg. PPD was used in two amounts, the first test dose being 0.000,02 mg. and the second test dose being 0.005 mg. Old Tuberculin, in amounts of 0.001 mg., generally gave a higher number of positive reactions than 0.000,02 mg. of PPD, but when the larger dose of PPD was used there was no significant difference in the final results. Readings were made at twenty-four and forty-eight hours after injection.

At the time of injection, inquiry was made concerning the student's previous history. This included age, previous habitat (urban or rural), presence or absence of tuberculosis in family and results of previous tuberculin tests, if any. Ninety-eight per cent of the students fell into the 20 to 24 year age group, the average being close to 23 years of age. The students at P. & S. are drawn from many parts of the country. About 15 per cent of them come from western or southern areas, about 18 per cent from New York City, and the remainder from suburbs of New York City or elsewhere in the eastern area. Their families are, for the most part, fairly well-to-do. Only occasional students (about one per cent of the total) reported cases of tuberculosis in the family and an insignificant number had had previous tuberculin tests. None of the students had been exposed to possible infection either in the clinic or at the autopsy table.

The results are presented in tables 1 and 2. It may be seen that, of all students tested between 1936 and 1944, an average of 67 per cent reacted, varying from a

<sup>1</sup> From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York, New York.

high of 81.4 per cent in 1936 to a low of 50 per cent in 1940. The senior author's recollection is that twenty years ago about 90 per cent of the students tested were positive. There seems to be a definite trend towards a decrease in the number of reactors, with the exception of the last year when higher figures were recorded. A search of the literature reveals only a few data of tuberculin reactions in second year medical students. Johns Hopkins (1) second year medical students, in

TABLE 1

*Tuberculin tests on second year medical students, P. & S., 1936-1944*

DATE	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
1936	54	44	81.4
1937	44	33	75.0
1938	80	62	72.5
1939	77	55	71.4
1940	76	38	50.0
1941	78	44	56.0
1942	101	63	62.3
1943	103	53	51.1
1944	87	64	73.5
Summary.....	700	466	66.5
Average.....	77.7	51.6	67.0

TABLE 2

*Tuberculin reactors according to habitat*

DATE	URBAN			RURAL		
	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive
1940	63	40	63.3	13	6	46.1
1941	47	23	48.8	19	6	31.5
1942	72	50	60.7	29	14	48.2
1943	76	54	71.0	27	9	33.3
Summary...	258	167	64.7	88	35	39.8

1930, were 77.9 per cent positive to tuberculin, while at the University of Pennsylvania (2) the figures for the years of 1930 and 1933, respectively, showed 94.2 per cent and 90.3 per cent reactors. It therefore seems evident that a definite decrease in the number of reactors among medical students has occurred in the years preceding the war, a tendency which has been reversed with the advent of wartime conditions in 1944. The average of 67 per cent tuberculin positives is slightly higher than the incidence of infection (60 per cent) in the same age group as reported by Rich (3). It may be noteworthy that Rich included in his table only those surveys in which the final test dose was 1.0 mg. OT, or its equivalent in PPD.

In table 2, where figures relative to previous habitat are given, it is seen that urban dwellers have an incidence of infection significantly higher than rural dwellers. This, of course, agrees with previous observations. Although rural dwellers form 25 per cent of those submitting to the test, even with the inclusion of this group, the total number of reactors among the students is relatively high. In spite of the marked reduction in morbidity and mortality from tuberculosis in this country, infection with the tubercle bacillus apparently is still relatively high in this age group of a selected portion of the population.

#### SUMMARY

Tuberculin tests on second year medical students over a period of nine years, using a maximum dose of 0.1 mg. of OT or the second test dose (0.005 mg.) of PPD, show that the incidence of infection among these students decreased from 81.4 per cent in 1936 to 50 per cent in 1940. Since 1940 an increase in incidence of infection has apparently occurred. The number of positive reactions in 1944 was 73.5 per cent of those tested. Of a total of 700 students tested during the nine years 1936-1944, 66.5 per cent reacted to tuberculin.

#### SUMARIO

Las reacciones a la tuberculina efectuadas en los estudiantes de segundo año, de una facultad de medicina, durante un período de 9 años, con una dosis máxima de 0.1 mg de TA o la segunda dosis de ensayo (0.005 mg) de PPD, revelan que la frecuencia de la infección entre dichos estudiantes descendió de 81.4 por ciento en 1936 a 50 por ciento en 1940. Desde 1940 aparentemente ha tenido lugar un aumento. El número de reacciones positivas en 1944 alcanzó a 73.5 por ciento en los comprobados. De un total de 700 estudiantes comprobados en el novenio 1936-1944, 66.5 por ciento reaccionaron positivamente a la tuberculina.

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## AMERICAN TRUDEAU SOCIETY

### Minimal Medical and Administrative Standards for Tuberculosis Hospitals and Sanatoria

#### A Report of the Committee on Sanatorium Standards

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These Standards are concerned principally with the minimal standards for medical administration. Standards for nonmedical administration are set forth in *Tuberculosis Sanatorium Planning*<sup>1</sup> and include recommendations as to number of beds needed; site; architectural requirements for medical, surgical, and service facilities; personnel quarters and utilities. The Committee on Sanatorium Standards recommends that, in contemplating the construction of a new hospital or sanatorium, a minimum capacity of 50 beds be considered. It is the opinion of the Committee that, in the interests of economy and efficiency in the administration of an active modern tuberculosis service, a capacity of not less than 150 beds is preferable. If standards and services are to be maintained, the smaller the institution, the greater the proportionate cost of salaries for department heads, and the greater the difficulty in obtaining qualified full-time medical superintendents and staff members and consultants necessary for proper functioning of the services. Where morbidity rates justify the establishment of smaller institutions, such units should be connected with the local general hospital.

#### I. ORGANIZATION

The primary function of every sanatorium is to serve the best interests of the patients. For most efficient operation, the sanatorium organization should permit of distinct delegation of responsibilities. A governing board of trustees, managers or directors, or some official charged with this duty, is necessary for the formulation of the policies of the institution. The medical superintendent, an appointee of the governing board, should solely be responsible to the board for the management of the institution and for the medical care and treatment of all patients. He must, therefore, be given proper authority by the board. All officers and employees should be appointed by him or subject to his approval, and be answerable to him.

Successful operation of a hospital depends upon the integration of its medical and nonmedical activities. The medical superintendent, trained in the treatment of the sick, and interested in the solution of medical problems, should delegate authority to a business manager in the administration of the nonmedical

<sup>1</sup> Published by the National Tuberculosis Association, 1939, and now undergoing revision.

affairs of the institution and hold him accountable for efficient performance. Frequent conferences between those two officers will enable the superintendent to keep in touch with significant developments and to guide in matters of policy, thus relieving him of many purely administrative burdens and conserving his time for professional work. In such circumstances, the integrity and ability of the business manager are of the highest importance.

## II. MEDICAL STAFF

The medical superintendent shall be a reputable licensed physician with at least three years' experience in a recognized tuberculosis institution, and, preferably, fully qualified in tuberculosis by the American Board of Internal Medicine. In institutions of 100 or more beds, the position of medical superintendent shall be full-time.

There shall be, in addition to the medical superintendent, at least one full-time resident physician for the first 100 resident patients, and one additional full-time physician for each 50 additional patients or the major fraction thereof.

Where the sanatorium assumes entire responsibility for the tuberculosis control service in the area, there shall be, in addition to the physicians required for the medical administration of the sanatorium, one full-time physician for each 100 resident deaths from tuberculosis, or major fraction thereof. The above ratio does not include pathologists or roentgenologists.

Each member of the resident medical staff shall be a graduate of a grade-A medical school and, preferably, shall have had a rotating internship in a general hospital.

The services of consultants in internal medicine, general surgery and in the medical and surgical specialties should be utilized. In the large institutions, laryngology, bronchoscopy, pneumonolysis and thoracic surgery should preferably be a part of the over-all full-time diagnostic and treatment services. In the smaller institutions where such facilities cannot be provided on a full-time basis, they should be made available through the services of consultants or by arrangement with other institutions where such work is done.

Meetings of the medical staff, including consultants, shall be held regularly, at least semi-monthly and preferably weekly, to discuss problems of diagnosis and treatment. It is also advisable to stimulate interest through seminars and journal clubs.

Medical education and research shall be encouraged. For purposes of study and reference, there shall be an amply supplied medical library.

The medical administration should maintain coöperative relationships with the local health authorities, the local tuberculosis associations and with the practicing physicians in the community. Contact with physicians from other sanatoria and teaching centres should be encouraged.

The attendance of the medical superintendent or other members of the medical staff at the meetings of the American Trudeau Society and the National Tuberculosis Association should be subsidized. Such meetings provide opportunity not only for obtaining knowledge from the formal papers presented but also for

invaluable private discussions with his colleagues. With this background he is in a far better position to evaluate critically and to discuss with his staff the findings in published papers than could ever be acquired from the mere reading of medical journals.

### III. MEDICAL SERVICES

Every patient should be seen by a physician within twenty-four hours of admission.

The initial physical examination shall include not only the chest and upper respiratory tract but the entire body.

Chest X-ray examinations shall be made on admission, as frequently as indicated in the course of treatment, and on discharge.

Patients who are acutely ill should be visited by the physician as often as necessary, but at least twice daily. All other patients confined to bed should be seen by the physician at least once daily. Ambulant patients should be seen at least twice weekly by the physician and daily by the nurse in charge.

Temperature, pulse and respiration should be taken at least three times daily during the first week and during the febrile phase, and thereafter three times daily at least one day a week.

Patients should be weighed once every two weeks unless contraindicated.

Physical examination of the chest should be made as often as necessary but at least every two months if the patient is doing well. X-ray examination should be made at least every two months if the lesion has been unstable, and more often if necessary. If the lesion has been more or less stationary over several months, the interval for physical and X-ray examinations may be increased to three months. The interval may be extended further for ambulatory patients under custodial care.

Progress notes regarding the patient's condition should be made at sufficiently frequent intervals to record significant changes in his clinical course and at the time of each examination.

Treatment of all kinds, general and special, including regulation of physical activities of patients, shall be prescribed and supervised by physicians.

Since rest is the basic treatment of tuberculosis, strict bed-rest should be available for all patients who need it, and definite periods of enforced rest for all others should be a part of the sanatorium routine. The amount and degree of rest should be prescribed for each patient in detail with all permitted activities and restrictions definitely specified.

Facilities shall be available for all approved collapse therapy procedures in order that the particular treatment best adapted to a given case may be chosen freely and instituted promptly.

All patients receiving pneumothorax should be fluoroscoped before each refill and adequate roentgenological guidance is essential to successful and safe management. In the early phase of pneumothorax treatment, each case should be reviewed monthly or more often if necessary to determine whether the collapse is satisfactory or can be made so. The report of the American Trudeau



Society Committee on Therapy, *Some Suggested Procedures for the Early Period of Pneumothorax*,<sup>2</sup> outlines the basic principles in the management of such cases. Pneumothoraces which cannot be made effective should be abandoned promptly and other appropriate treatment instituted. In the course of treatment by pneumothorax, periodic review is necessary to determine the optimum time for reëxpansion or substitution of other therapy.

Associated tuberculous and nontuberculous conditions should receive appropriate attention.

Adequate dental services should be furnished at the sanatorium.

The medical records of patients shall include the following: Admission history, social and medical history, results of physical examinations, X-ray and fluoroscopy interpretations, laboratory findings, treatments given, reports of consultations and staff meetings, progress notes, surgical and anesthetic data, diagnosis, results of postmortem examinations and the condition on admission and discharge. All entries shall be dated and signed by the physician concerned.

The clinical classification of patients on admission and discharge shall be made in accordance with the Diagnostic Standards of the National Tuberculosis Association.

#### IV. THE CARE OF CHILDREN

Children with clinically active tuberculosis should be treated in a separate building or in a separate ward of the building for adults. Provision should be made for supervised play and for education, so that, after their discharge, these children may take their place in the community with others of their own age. Preventoria, as such, have no place in the modern treatment of tuberculosis.

#### V. ROUTINE LABORATORY PROCEDURES

A complete microscopic blood examination of each patient should be made as soon as practicable after admission. Hemoglobin estimations, red cell sedimentation tests and a recognized test for syphilis should also be performed.

Examinations of sputum for the presence of tubercle bacilli should be made in accordance with methods recommended by the *Approved Minimum Standards of Laboratory Technique* as prepared by the American Trudeau Society Committee on Evaluation of Laboratory Procedures. Laboratory methods have been so refined that tubercle bacilli are now found in the sputum of a large proportion of tuberculous patients. It is the responsibility of the clinician to interpret the sputum report in the light of the total clinical picture. For guidance in therapy, discharge or follow-up, the clinician must relate the laboratory report to the rest of the data available. If the laboratory reports the method employed as well as the result of the test, the clinician has additional valuable data. Sputum found to be positive by direct smear or by culture of gastric washings only may have totally different significance for the physician in charge of the case.

All patients in whose sputum or discharges tubercle bacilli have not been found should be tuberculin tested by the intracutaneous method.

<sup>2</sup>Am. Rev. Tuberc., 1944, 50, 573.

A clinical and microscopic examination of the urine of newly admitted patients should be made to note twenty-four hour output, specific gravity, sugar, albumin, blood and pus cells, casts bacteria, etc. If any of these tests are positive, further studies should be made as indicated. All specimens which show albumin, red or white cells, or a combination of these, should be examined for tubercle bacilli by culture or animal inoculation, using twenty-four hour specimens. If urinalysis is negative, routine reexaminations of the urine are scarcely worth the effort unless symptoms develop or some other indication appears.

Pleural exudates and pericardial or peritoneal effusions, pus from ears, cold abscesses or sinuses, feces, spinal fluid, gastric washings, and biopsy specimens should be examined for tubercle bacilli when indicated, in accordance with the methods recommended in the report of the American Trudeau Society Committee on Evaluation of Laboratory Procedures.

Every effort should be made to secure permission for autopsy of patients who have died at the institution, in order to attain at least the minimum standard of autopsies of 15 to 20 per cent of all fatal cases, as recommended by the American College of Surgeons for general hospitals.

#### VI. NURSING SERVICE

The director of nursing, assistant director of nursing, supervisors and head nurses should be registered in the state in which the sanatorium is located and, in addition, must have had special instruction and experience in tuberculosis nursing. Provision should be made for new members of the general duty nursing staff who have not had instruction and experience in tuberculosis nursing, to receive at least a short technical course with follow-up supervision.

Good isolation technique shall be used and adequate equipment for this purpose should be provided. Nursing service shall be properly adjusted with respect to the proportion of infirmary, semi-ambulant and ambulant patients, the ratio of nurses for whom shall be not less than 1:3, 1:8 and 1:30, respectively. This is for twenty-four hour coverage. If thoracic surgery is done at the institution, the ratio of nurses to patients recently operated upon should be not less than 1:2. In calculating ratios of nurses to patients, suitable credit may be given for services performed by orderlies, nursing attendants or other well-trained auxiliary workers.

#### VII. HEALTH SUPERVISION OF NURSES AND OTHER EMPLOYEES

All nurses and other employees should have, at the time of employment, an initial complete physical examination which should include a tuberculin test, chest X-ray examination, Schick test and appropriate laboratory studies. They should be vaccinated against smallpox. Those with a history of typhoid fever should have stool examination for typhoid bacilli. All employees should be offered a complete annual physical examination.

A comprehensive program of health supervision should be maintained for all nurses and other employees who have close association with patients or work in patients' rooms, laboratories or otherwise are exposed to tuberculosis. They

should be encouraged to observe good personal health practices in order to keep their resistance at a high level. They should not work more than eight hours daily and should have one day off out of each seven. Accumulated time off should be discouraged and should be allowed only in special instances. After the first year of service, a minimum of two weeks' vacation annually with pay should be given. A definite amount of sick leave with pay should not be specified but a minimum of two weeks per year should be allowed.

Proper housing, adequate diet and recreational facilities should be provided for all resident employees.

Nurses and other employees who are in contact with patients, patients' rooms, laboratories or fomites should be X-rayed every three months. This interval may be extended to six months in the case of tuberculin-positive nurses and employees who are past the age of 30. Those who are tuberculin-negative should be retested and X-rayed every three months.

Those employees who do not have contact with patients, patients' rooms, laboratories or fomites should be X-rayed every six months; if tuberculin-negative, they should be retested every six months.

#### VIII. SPECIAL SERVICES

The social service needs of patients are of utmost importance. Unless adequate provision is made for such service through accepted existing agencies, sanatoria should employ a full-time social worker for each 200 patients or major fraction thereof.

Provision should also be made for the religious needs of the patients.

Adequate provision should be made for recreation and for occupational therapy. In institutions of 150 beds or more, the employment of one or more full-time registered occupational therapists is recommended.

If children are accepted for treatment, adequate provision should be made for the continuation of their education. Instruction in high school subjects should be available to adolescents when the number of patients in this category is sufficient to warrant it. Adequate educational facilities for all patients within the institution are desirable. They should include a library with a service for bed patients. The instruction of each patient during hospitalization should be correlated with his physical condition, and his study time observed and recorded by the educational staff.

In institutions of 200 bed capacity or more, a formal educational and rehabilitation program is desirable. This might be accomplished by coordinating the work of school teachers, occupational therapists and medical social workers. The staff should include preferably a resident counselor in vocational education and rehabilitation, with training at the professional level. In the absence of such a counselor as, for example, in the smaller institutions the need could be met partially through cooperation with state vocational services. Efforts at rehabilitation should begin as soon as possible after the patient's admission. Each patient discharged with medical consent whose rehabilitation has not been

planned otherwise shall be advised fully regarding the rehabilitation and placement services available in the community to which he is to return.

Systematized adequate instruction should be given patients with regard to tuberculosis as a personal and community problem, that is, prevention and general principles of treatment.

Post-sanatorium follow-up of the discharged patient is valuable and should not be neglected.

#### IX. SALARIES

Permanent competent medical personnel should be adequately remunerated. Suggested yearly cash salaries, in addition to maintenance, are listed below:

	For hospitals of 100 beds or less	For hospitals of 200 beds or more
Superintendent (medical).....	\$5000-6000	\$6000-8500
Assistant superintendent (medical).....	—	5500-8000
Thoracic surgeon.....	—	5500-8000
Pathologist.....	—	4000-5000
Roentgenologist.....	—	4000-5000
Senior resident physician or surgeon.....	—	4000-5000
Assistant resident physician or surgeon....	3000-3600	3000-3600
Junior resident physician or surgeon.....	1800-2400	1800-2400
Superintendent of nurses.....	2000-2500	2500-3000
Assistant superintendent of nurses.....	—	2000-2500
Supervisors or charge nurses.....	1800-2100	1800-2100
Graduate nurses.....	1400-1800	1400-1800
Undergraduate nurses or nursing attend- ants or assistants.....	900-1200	900-1200



# TUBERCULOSIS AS A MILITARY PROBLEM<sup>1,2</sup>

ESMOND R. LONG<sup>3</sup>

Much has been written about tuberculosis as a military problem. The disease has been a significant one as an impediment to military operations, for it has always constituted a leading cause of disability, has added appreciably to the noneffective rate, has required the time and effort of medical officers in taking care of cases, and has tied up transport facilities sorely needed for evacuation of battle casualties.

## TUBERCULOSIS IN PREVIOUS WARS

The United States Army has maintained records of tuberculosis hospital admissions and discharges since the Civil War. An illuminating account of tuberculosis as a war problem is given in the Medical and Surgical History of the War of the Rebellion, prepared under the direction of The Surgeon General, United States Army, and published in 1888. Present day accuracy in compilation of statistics was not possible at that time, but it is interesting to note that figures were carried both for tuberculosis admissions to hospitals and for tuberculosis discharges. During five and one-half years of military mobilization and operation, 13,499 cases of tuberculosis and 5,286 deaths were reported in white soldiers. These figures yield an admission rate of 6.1 and a death rate of 2.2 per thousand strength per year. That all cases ultimately discovered, however, were not reported as admissions is shown by the fact that 20,403 white soldiers were discharged for tuberculosis. This means that there were 12,190 more discharges than admissions, exclusive of those who died of tuberculosis. The mean annual rate of discharge for tuberculosis in the Army was 8.4 per thousand strength for whites. The rate was much lower in colored soldiers, namely 3.1 per thousand.

In the short Spanish-American War an appreciable rise in the tuberculosis admission rate was recorded, and the increased rate persisted for some years after the war. For the decade prior to the war the average rate was 2.7 per thousand strength per year. In 1898, following call of the National Guard to duty and accelerated enlistment, the rate rose to 3.7. In the following year it was 4.0 and in 1900 4.9.

Tuberculosis was a problem of outstanding importance in World War I, recognized as such in all armies. In the United States Army its significance was first appreciated after reports were received of a huge incidence in the

<sup>1</sup> Reprinted from The Proceedings of The Institute of Medicine of Chicago, February 15, 1945, vol. 15, pp. 241-255. Republished with the permission of the Committee on Publications of The Institute of Medicine of Chicago.

<sup>2</sup> Ninth Christian Fenger Lecture of the Institute of Medicine and the Chicago Pathological Society, January 8, 1945.

<sup>3</sup> Colonel, Medical Corps, Army of the United States, Chief Consultant on Tuberculosis, Office of The Surgeon General, War Department, Washington, D. C.

French Army. The fact was widely publicized that within five months after the outbreak of the war the French medical military service had returned 86,000 soldiers to civil life with a diagnosis of active tuberculosis. By February 1917 the reported number had risen to 150,000, and it was said that large numbers of exchanged prisoners of war were returned to France suffering with tuberculosis. While, later, doubt was thrown upon the accuracy of these figures, there was no question that the problem was one of considerable magnitude. Shortly after the United States entered the war The Surgeon General decided to have the United States Army reexamined for tuberculosis by the best available experts. Examinations began in July 1917. The methods of examination, as we now know, were not sufficiently accurate to exclude more than a minority of cases of minimal tuberculosis. X-ray examination was available on an extremely small scale only, and the equipment was highly inferior to that used to-day. Hence large numbers of men with tuberculosis escaped discovery, and their acceptance is reflected in a relatively high admission rate in succeeding years. The average admission rate in terms of men per thousand strength per year for the period of the war was approximately 12.0. The average annual discharge rate was 5.7, or about half of the admission rate, a proportion holding fairly well to-day. Throughout World War I tuberculosis was the leading cause of discharge for disability, accounting for 15 per cent of all discharges.

Studies of the type of tuberculosis in the different armies in World War I yielded information of noteworthy pathological significance. The predominant type discovered in American troops was chronic ulcerative pulmonary tuberculosis, no different in character from that observed in the civilian population of comparable age. In conspicuous contrast was the rapidly progressive, exudative pulmonary tuberculosis, accompanied by manifestations of widespread generalization, seen in Senegalese troops sent to Southern France. Colonel Bushnell, chief consultant on tuberculosis in the Office of The Surgeon General of the United States Army, wrote exhaustively on the subject. He attributed the differences to fundamental variability in acquired immunity. American troops were believed to represent a group already infected, whose subsequent tuberculosis was conditioned by their previous infection, and therefore of the well known chronic reinfection type, characterized by fibrosis and cavity formation. It was the considered view of American medical officers that the great majority of cases developing in troops represented tuberculosis that was present but undetected at the time of induction. In the Senegalese troops, on the other hand, according to Colonel Bushnell's belief and that of others who studied the subject, the infection represented first infection in a body of soldiers with little previous experience with tuberculosis. Surveys on colored troops arriving in France showed that a high percentage was tuberculin-negative. There is little doubt that this group of colored troops suffered from massive primary infection. The fact that they represented an unselected stock, which had not had the supposed benefits of civilization in wiping out human strains most susceptible to tuberculosis, was generally overlooked by writers of the period.

## EXCLUSION OF TUBERCULOSIS FROM MILITARY SERVICE

Exclusion of tuberculosis from the Army in World War I was carried out, as well as possible, by the method of physical examination. Auscultation of the chest was skillful and possibly superior in character to that practiced to-day. It was far inferior, however, in the detection of tuberculosis to modern X-ray methods. At the outbreak of the present war it was apparent to the Office of The Surgeon General of the United States Army that the method used in World War I could not be counted upon to be effective in an Army of the expected size of ours. It is interesting to note, in the large literature on tuberculosis as a military problem, the stress laid on general physical habitus, minor differences in shape of the chest, and physical signs on auscultation and percussion, as well as the emphasis on history of tuberculosis in the family and ancestors. While all these are of importance to-day, their significance shrinks in the face of a vast problem requiring rapid, accurate examination of large numbers of recruits. In a modern army of millions, exclusion of tuberculosis is utterly dependent upon mass X-ray methods. Without such methods tuberculous subjects would be accepted in number approximating the incidence of minimal tuberculosis in the population of corresponding age. In the United States this would be not less than one-half of 1 per cent, and possibly as much as 1 per cent in men above 25 years of age.

For this reason the physical standards drawn for the detection of tuberculosis in World War II, in marked contrast to those laid down in the famous directive, Circular No. 20, from the Office of The Surgeon General in World War I, were devoted almost exclusively to X-ray evidence of tuberculosis, and, while physical examination of the chest is an integral part of induction station examinations, maximum reliance is placed on the X-ray picture. The standard method, employed throughout the country in induction stations, is photoroentgenography. Stereoscopic 4 by 5 inch films are used, and it is of interest to note that the technical quality of these has improved immensely since the beginning of mobilization.

It may be observed here that photoroentgenography is now widely used in mass surveys in other armed services. It is employed by the United States Navy routinely in surveys of its personnel, and by the Royal Navy in Great Britain. Both navies use 35 mm. film. It is of interest that in the Royal Navy photoroentgen examination of nearly half a million apparently healthy men not previously screened by X-ray examination, showed an incidence of 1.27 per cent with tuberculosis. In 47.9 per cent of cases the lesion discovered was of minimal extent. The German Army is said to have used the same method as a routine measure, but the results of its examinations are not known to our Army. In other armies the method is already used more or less extensively or in the course of introduction.

Induction standards require that all active tuberculosis of the lungs, as well as tuberculosis of any other organ, be excluded. The small well scarred infiltrative lesions, so common in the upper part of the lungs, were recognized at the onset as constituting a special problem. Many such scars are known to be stable, while others are of doubtful prognosis. The rule adopted, which



has worked fairly well, is that small, sharply limited, fibrous or nodular lesions, not exceeding an area of 5 square centimeters in flat plates can be accepted after a period of deferment of not less than six months, if reëxamination after that time fails to disclose any change in their character or extent. Hundreds of men have been taken into the Army with such lesions, and from the knowledge gained as to their subsequent course, much information ultimately will be made available on the pathogenesis of chronic pulmonary tuberculosis. Already we know that some of the lesions in question have broken down. Up to the present, however, available evidence indicates that in the majority of cases judgment was good and the men have held up in spite of prolonged work and heavy hardships. An investigation is under way, fostered by the Committee on Medical Research of the Office of Scientific Research and Development, and the Division of Medical Sciences of the National Research Council, in which a study is being made of a thousand cases of minimal tuberculosis in men from many branches of Army service. An interesting finding thus far is that breakdowns appear to have been approximately as frequent in men in sedentary occupations as in men who have engaged in severe combat. A gratifying fact is that in many instances years have been spent in occupations with vigorous activity without demonstrable change in the X-ray appearance of the lesions in question.

Because of the conspicuous character of calcified primary lesions, detailed reference to such lesions was necessary in mobilization regulations. Furthermore, because of the still existing uncertainty as to the relative rôle of endogenous and exogenous infection in tuberculosis in adult life, those drawing the regulations had to take into account both possibilities. For this reason, in the early days of the war, in editions of mobilization regulations then current, possibly undue emphasis was laid upon the calcified primary lesions. In the first months of mobilization, that is, in 1940 and 1941, as X-ray examination became more widely used in induction stations throughout the country, innumerable queries reached the Office of The Surgeon General as to the acceptance or rejection of men with large and multiple calcified scars. In the lack of a more rational standard, in the regulations in effect when war was declared, arbitrary limits in terms of size and number of lesions were drawn as a guide for induction station officers. At a later period, with gathering knowledge of the stability of these lesions and gain in experience by induction station medical officers, it became possible to return to the original intention, and base acceptance of men with such lesions upon medical judgment, expressed in the light of both X-ray examination of the chest and the general health of the patient, including any other evidence of tuberculosis.

The problem of calcification is temporarily in abeyance. Most men who were rejected in the early days of the war because of large or numerous calcified lesions have been brought again to induction stations and subjected to reëxamination. In the light of current opinion on the stability of these lesions, a large percentage of these men have been accepted for military service. Thus far we have no evidence that any has broken down through

reactivation of a calcified primary lesion. A few statistical studies have been initiated on men rejected for large calcified primary lesions. None of these has as yet been published. In general they show little difference in the rate of development of tuberculosis in men with and men without large calcified lesions. It is generally agreed that in the groups studied extraneous factors, such as contact with other cases of tuberculosis, must be fully as important as the presence or absence of tubercle bacilli in the lesions in question.

Current experience is comparable to that of World War I in that the majority of cases of tuberculosis that have developed have been in men who proved to have evidence of existing tuberculosis at the time of induction. The highest admission rates that have occurred were in the early months of mobilization, following a period when men in some parts of the country were accepted without X-ray examination. After preinduction chest X-ray examination became universal, about April 1, 1942, the rate of admission for tuberculosis dropped sharply. With improving work in the induction stations it has continued to decline slowly but steadily. It is still not possible, under the conditions of rapid mobilization, to exclude all minimal cases. Cases are admitted occasionally in spite of the best efforts of induction station radiologists. In the majority of cases of tuberculosis discovered in the Army, comparison with the induction film shows that a lesion was present on acceptance.

Approximately 150,000 men have been rejected at the armed forces induction stations, half of whom had lesions believed active at the time of the examination, the others being considered as potentially active under military strain. In 1943 a sampling in The Surgeon General's Office on more than 50,000 induction chest X-ray films of men inducted in the summer of 1942, made in order to determine how much tuberculosis had been overlooked, indicated that from 10 to 15 cases per 10,000 men, with visible lesions, failed of detection in the induction examination. Various difficulties, chiefly the speed of examination, were believed to account for the errors. The admission rate in the Army in subsequent years has borne out this estimate with remarkable fidelity.

#### ARMY ADMISSION RATES FOR TUBERCULOSIS

Nothing illustrates more clearly the value, and at the same time the limitations, of preinduction X-ray examinations than a comparison of the admission rates for tuberculosis in World War I and World War II. These are shown in the accompanying figure 1, which shows that the rate for World War I was approximately 10 times that for World War II. It must not be assumed, however, that the difference is entirely due to improved methods of detection in the second World War. Less cases, relatively, were to be excluded in the second war, for the incidence of tuberculosis in the general population at the present time is approximately one-third of that prevailing in the period of World War I.

The peaks in the curves shown are of interest. In each war an early peak occurred, which is believed to reflect imperfection in examination, whether that was physical or by X-rays. Improvement occurred rapidly in physical

# TUBERCULOSIS, ADMISSIONS PER THOUSAND MEN PER YEAR

ARMY IN THE CONTINENTAL U.S.

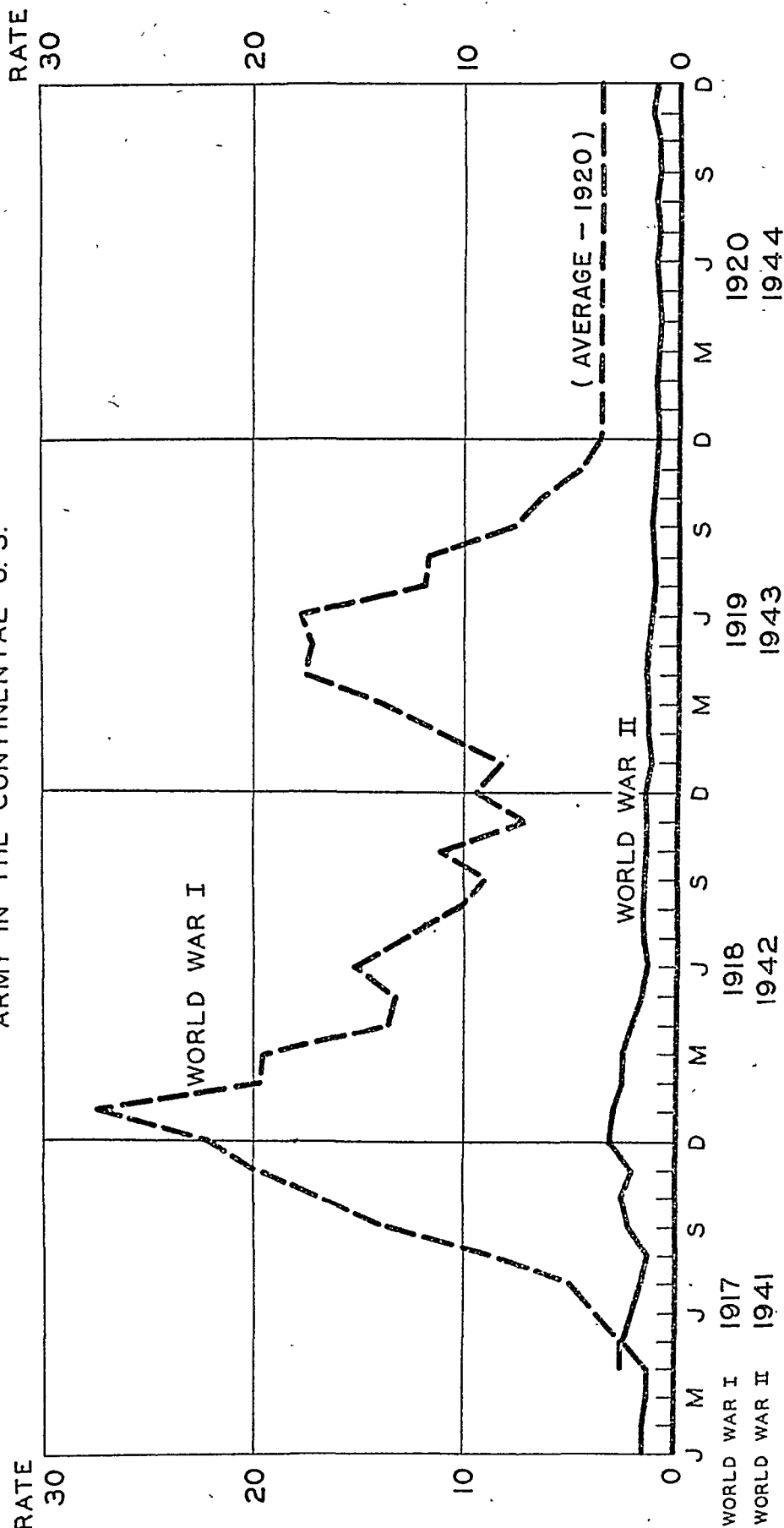


Fig. 1

Note. The two charts have been completed through the last two months of 1944

methods in World War I and in the frequency of use and accuracy of X-ray methods in World War II. The second peak in the World War I record represents cases of tuberculosis discovered in the discharge examination. It may be presumed that a somewhat similar rise will occur on demobilization of the Army in the present war. It is hoped, however, that the peak will not be so high, because periodic examinations have discovered many of the existent cases.

Attention is called again to the difference between admission and discharge rates. These are roughly parallel, as the accompanying chart (figure 2) shows,

### TUBERCULOSIS ADMISSIONS AND DISCHARGES RATES PER THOUSAND MEN PER YEAR

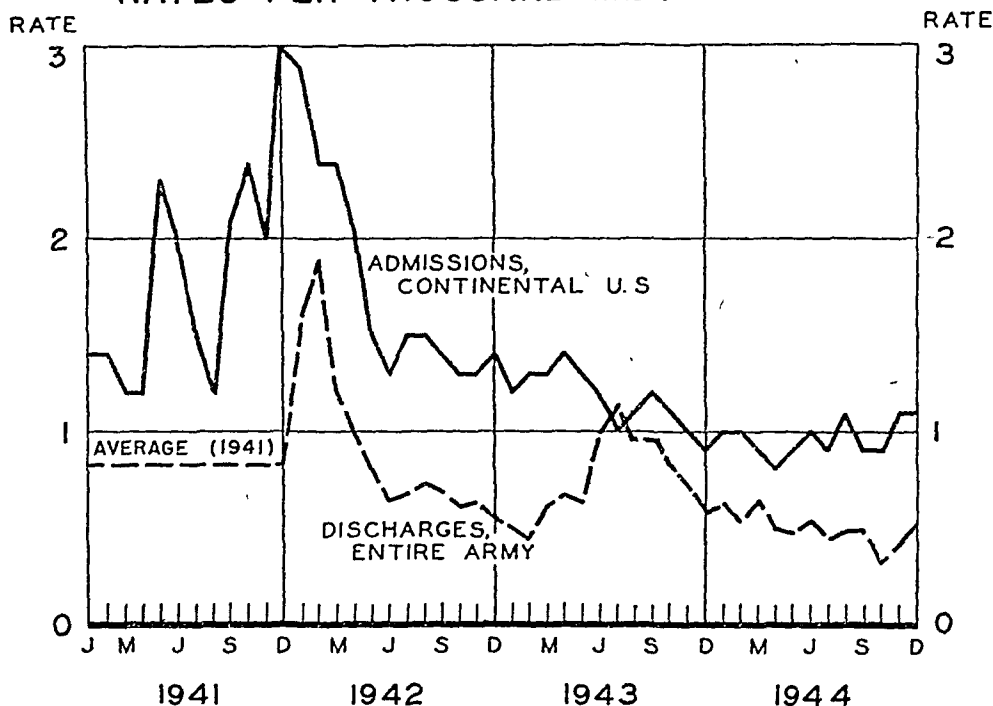


FIG. 2

the discharge rate representing from half to two-thirds of the admission rate, except for an occasional explainable peak when it surpasses it. In general the difference in the curves is explained by the fact that only half to two-thirds of the cases examined prove to be active or of such character as to indicate potential activity. The remainder are ultimately considered stable, or the scars in question are considered nontuberculous and the men are returned to limited or full duty. Occasional humps in the discharge rate represent accelerations of discharge in accordance with current directives. One such peak is evident in the late summer of 1943, when a directive, with a view to general improvement in the physical quality of the Army, was issued which led to the mass discharge of many men with lesions of probable stability who

were performing limited service. The high discharge rate in early 1942, paralleling the high admission rate at that period, is reasonably attributed to the influx into the Army of a considerable number of men who had not had X-ray examinations prior to acceptance. The great majority of these men were X-rayed subsequently, and those with tuberculosis promptly discharged.

#### EXOGENOUS AND ENDOGENOUS INFECTION

A principal problem, to which reference already has been made and which will be the subject of extended research after the war, when immediate military demands are less pressing, is that of the exogenous or endogenous origin of cases of tuberculosis discovered in the Army. Obviously this problem is of great military importance, for it involves the question of exposure in the lands to which our troops are sent.

In this connection the reported experience of the Canadian Army is of interest. Colonel Adamson and Captain Keevil of the Royal Canadian Army Medical Corps have reported a change in the incidence of tuberculosis in Canadian troops since the outbreak of the war that appears to them to be of great pathological significance. During 1939 and 1940 very little tuberculosis was evident in Canadian troops. All the men had been X-rayed and tuberculosis had been well excluded. In the summer of 1941 an abnormal number of cases of pleurisy with effusion was reported in troops overseas. The rise and unexpected incidence of pleurisy was not evident in troops in Canada. According to figures presented, the rise was greatest overseas in troops who had come from regions where the incidence of tuberculosis in the population was lowest. The conclusion reached was that after two years of war an increase of primary tuberculosis was occurring, resulting from exposure overseas, and chiefly manifest in men who had not had the immunizing influence of a primary infection in their home communities. Colonel Adamson and Captain Keevil believe that the wave of pleurisy with effusion is now on the wane, and explain the decline on the basis of a more nearly completed "tuberculization" of the Canadian Army. Even in Canada, however, the statement is made that "the cases which have arisen in the Army up to now are the fruition of infection that took place before enlistment." (*J. Canad. M. Sciences* 1:404, 1944.)

In the United States Army up to the present time no rise comparable to that experienced in the Canadian Army has occurred. Periodic surveys in the Office of The Surgeon General, in which comparison is made of discovered cases of active tuberculosis with induction films, have shown in the great majority of instances that the lesion finally discovered represents an extension from a minimal lesion missed at the time of acceptance for military service. Thus far, although representing the onset of a significant proportion of the total cases of tuberculosis, tuberculous pleurisy with effusion is a relatively minor cause of hospital admission among American troops, and no increase in the incidence of cases has been reported. The admission rates per

thousand men per year for serofibrinous pleurisy with effusion in 1942 and 1943 were as follows:

1942		
	Continental U. S.	0.36
	Overseas	0.26
1943		
	Continental U. S.	0.25
	Overseas	0.25

As indicated above there has been as yet no increase in extent or change in character of tuberculosis attributable to the strain and exigency of a long war. However, it must be recognized that in an army as widely scattered as ours final compilation of figures may bring to light much information not yet available, and the ultimate discharge of patients may yield information not available through current reports.

A few minor suppressed "epidemics" of tuberculosis have been reported. Occasionally a document from overseas discloses an unexpected incidence of tuberculosis in a small unit. Whenever such incidence is discovered, all men in the outfit are X-rayed. It is interesting to note that, not infrequently under such circumstances, the men themselves are so well informed on tuberculosis, presumably as a result of the educational campaign in this country, that they themselves ask for X-ray examination. Few cases are so discovered.

#### DISPOSITION OF CASES OF TUBERCULOSIS

The disposition of cases of tuberculosis raises an important military problem. It must be recognized that the principal objective of an army hospital is care of patients with a view to returning them as rapidly as possible to duty. For those cases in which the likelihood of return to duty is remote and prolonged care is obviously necessary, another agency has been established by the Government, namely, the hospitals of the Veterans Administration. The fundamental principle applying in the case of active tuberculosis in the Army is to discharge men to appropriate care elsewhere as soon as is consonant with the principles of good medicine. In rare cases only is it believed that a man who has been discovered to have active tuberculosis in this war will be able to return to military duty during the course of the current conflict. Therefore, it is anticipated that with rare exceptions all active cases will be discharged. Provision is made by law for their prompt transfer to the Veterans Administration for care, and that Administration has a large number of hospitals designated chiefly for tuberculosis and extra beds for tuberculous cases in other general hospitals.

The Army directive now in effect provides that men will be discharged to the Veterans Administration as soon as practical after their unsuitability for further military service is established. There is an important proviso in the regulation, however, namely that men will not be discharged at an early period following diagnosis if such discharge is considered prejudicial to their

recovery. In effect this means that a large percentage of cases are held for definite treatment, leading to some degree of stabilization, before discharge. All tuberculous enlisted men from overseas are sent to one Army general hospital, Bruns General Hospital, near Santa Fé, New Mexico. Cases within the United States have either been handled locally, in station and general hospitals, or transferred to Fitzsimons General Hospital in Colorado, prior to discharge to a Veterans Administration facility. At these special tuberculosis hospitals, and at the station hospitals where tuberculosis is first discovered, an earnest effort is made to educate tuberculous soldiers on the need for continuing care after they leave the service.

In the first three years of war, from December 7, 1941, to December 7, 1944, approximately 10,500 cases of tuberculosis have been discharged from the Army. About 2,000 patients with tuberculosis are still resident in Army hospitals. Discharges for tuberculosis represent about 2 per cent of all discharges.

It is interesting to note that, relatively speaking, tuberculosis is much less of a problem in the Veterans Administration than it was in World War I. The annual report of the Administrator of Veterans Affairs for the fiscal year ended June 30, 1943, points out that at the close of that year 8.8 per cent of patients in their hospitals were under treatment for tuberculosis as compared with 64 per cent for neuropsychiatric disease and 27.2 per cent for general medical and surgical conditions. On June 30, 1923, 41 per cent of the patients in veterans' hospitals were tuberculous, 39 per cent were neuropsychiatric, and 20 per cent were of general medical and surgical classification.

#### TYPES AND FATALITY OF TUBERCULOSIS

The majority of tuberculosis discovered in the Army is pulmonary. For the first nine months of 1943, in the Army overseas, 90.9 per cent of the cases admitted to hospital by reason of tuberculosis were for pulmonary tuberculosis and 9.1 for nonpulmonary tuberculosis. The latter were chiefly cases of tuberculosis of the external lymph nodes, genito-urinary tuberculosis, and tuberculosis of the bones and joints, in the order named.

Death rates from tuberculosis in the Army are not of great significance. Since Army policy requires the discharge of cases as soon as practicable after diagnosis, with a view to continued care by the Veterans Administration, relatively few cases run a prolonged course in the Army. Army directives provide, however, that moribund cases will not be discharged. In the whole Army during 1941, 1942, and 1943 the provisional death rates per thousand strength for all forms of tuberculosis were recorded respectively as 0.044, 0.032, and 0.033. The respective rates for respiratory tuberculosis only were 0.032, 0.022, and 0.022. In other words the death rate is approximately 3.3 per hundred thousand, which may be compared with the current death rate of 50 per hundred thousand for the same age group in the civilian population.

#### OVERSEA PROBLEMS

Tuberculosis is quantitatively a smaller problem overseas than in the United States, judged by experience up to the present time. The lower rate

overseas is due to the fact that men have an initial screening before they are transported to a theater of combat. They are not given a complete resurvey for tuberculosis, including X-ray examination, but all must have a physical examination before proceeding overseas and in the course of this survey X-ray examination is made whenever there is reason to suspect tuberculosis. In addition, the fact must be recognized that several months elapse between induction and transport overseas, and that in this period most active cases come to light on a symptomatic basis. During this period men have a period of rigorous training, with opportunity every morning to report on sick call. Actually, experience has shown, however, that the majority of cases of tuberculosis discovered have been through some form of routine mass examination, as, for example, examination for officer candidate school, examination for flying status, or examination on transfer to a new type of duty.

A problem not yet wholly evaluated is that of infection from the civilian population overseas. In view of the very low rate of active tuberculosis in the Army, the opportunity for infection from a soldier's mates is almost negligible. As mentioned above, on rare occasions minor epidemics are said to have occurred, and in these cases prompt measures have been taken to determine possible sources of infection. The number of such epidemics reported could be counted on the fingers of one hand. Infection from the surrounding population is always difficult to determine. Its likelihood depends upon the intimacy of contact. The degree of intimacy is largely a personal matter and hard to evaluate on a large scale. The intimate and private contacts of soldiers can never be fully known. Presumably the opportunities for tuberculous infection through exposure in different populations are in direct proportion to the extent of open tuberculosis in those populations. If, however, soldiers' contact with a population in general is small, the total exposure will be slight. This is probably the case as respects the population of the Pacific islands, over which our troops are widely scattered. The tuberculosis rate in these island populations is high, but the troops' contact with natives is relatively low. The same is true in India and China, where the tuberculosis rate is very high. Language and other difficulties prevent such widespread intimate contact as may be the case with a surrounding population in this country.

In England and France, on the other hand, where billeting is more widely practiced, there is more opportunity for household exposure to tuberculosis. Fortunately, however, the rate of tuberculosis in the population of those countries is much smaller than in the other areas where our troops are engaged. As indicated above, thus far there has been no indication that exposure to endemic tuberculosis in the regions of oversea service has contributed measurably to the incidence of tuberculosis.

In certain places the question of bovine tuberculosis is to be considered. The American forces are forearmed in this respect. The relatively high incidence of bovine tuberculosis in England and Scotland is well known. With this in mind instructions were issued in the European Theater of Operations, by the Veterinary Corps of the Army, as early as September 5, 1942, stopping



the purchase of milk in the command unless the source could be approved under rigid Army regulations covering the requirements for milk for troop consumption. Since there are relatively few approved sources, Army hospitals have taken the bulk of approved milk available. At a later period the Red Cross stopped the purchase of milk from local sources for use in their canteens off military reservations.

Since a close association is recognized between bovine tuberculous infection and nonpulmonary tuberculosis, it is of interest to compare the rate for tuberculosis of other organs than the lungs in American troops in the British Isles with that in troops in the United States. Comparative figures are thus far available only for 1943. These show an admission rate for nonpulmonary tuberculosis in our troops in the British Isles almost identical with that for troops in this country. It is evident that if milk from tuberculous cattle is a source of danger to our troops in the British Isles, untoward effects were not evident up to the beginning of 1944.

#### EVACUATION

The evacuation of tuberculous patients presents a special problem in that it is not always possible to evacuate them by ideal means. In evacuation from foreign theaters, it is essential that proper provision be made for casualties requiring surgical treatment and litter transport and care. Insofar as possible, patients with active tuberculosis are not transported during febrile periods. Effort is made overseas to hold them until acute manifestations have subsided. Subsequently evacuation is by litter in the most serious cases, but a fairly high proportion of cases are ambulant. As soon as the patients arrive in port in the United States, classification is again made and cases which should be transported by litter are so carried.

Transportation in the United States is subject to state laws on the transport of patients with infectious disease. In effect these laws make it necessary for the Army to transport its tuberculous patients, from port to hospitals designated for their care or from one hospital to another or from a hospital to a Veterans Administration, in convoy. In this way closed space may be secured and attendants provided in a relatively economical manner.

At the present writing transportation by air is increasing. Since Pearl Harbor day more than 425,000 sick and wounded patients of the United States and allied forces have been evacuated by air. More than 6,000 patients have been flown from American ports of debarkation to Army hospitals in the interior. This includes casualties arriving by sea as well as those coming in by air. Many tuberculous patients are now transported both to this country from oversea theaters and from ports to points of care. Transportation is speedy and relatively comfortable.

A special problem in the treatment of tuberculosis arises in connection with air transportation. Intrapleural gas doubles in volume at 18,000 feet, and proportionate increases take place at lower altitudes. Unless care is taken to insure against excessive pressure, adhesions may be torn and other untoward results may occur from transport from low to high altitudes. This

problem is of importance not only in air transport but in transportation from sea level to such hospitals as Fitzsimons, 5,000 feet above sea level, and Bruns General Hospital, 7,000 feet above sea level. The problem has been given much study, and it is believed that untoward results are very rare. Occasionally, in transport to the United States, to avoid storms or detection by the enemy, flight at high levels is practiced. Customarily, however, transportation is at the relatively low level used in commercial flying.

Ordinary cases of pulmonary tuberculosis without pneumothorax do not appear to suffer ill effects from moderately long journeys by air. The Office of the Air Surgeon has sent a memorandum to the Office of The Surgeon General reading as follows:

"With respect to transportation of tuberculous cases, experience gathered during the past 24 months has shown that patients whose medical condition warrants movement suffer less shock and embarrassment when moved by air than by other means of transportation. Patients with active pulmonary tuberculosis have been flown for long distances at altitudes of 20,000 feet or more (with constant use of oxygen) without ill effect. Air movement of patients is routinely carried on at altitudes between 2,000 and 8,000 feet, except when weather, terrain, or military operations force the planes to higher altitudes.

"Sound medical judgment of the responsible medical officer in each individual case must remain the final answer as to suitability for movement of tuberculous patients."

#### TREATMENT OF TUBERCULOSIS

The treatment of tuberculosis is carried out by recognized standard methods. In the Army definitive treatment by collapse therapy is not practical in advanced areas, and is not carried out unless special circumstances, such as rapid excavation and hemoptysis, make it necessary. Ordinarily treatment is deferred until hospitalization can be effected within the United States. If it is anticipated that a patient will be discharged at an early period to the Veterans Administration, such definitive treatment as collapse therapy is ordinarily postponed until discharge is consummated. In other cases, however, where it is anticipated that the patient may be held for some months pending discharge, pneumothorax and other measures are instituted when they appear indicated. The procedures differ in no essential way from those in practice in our best modern sanatoria.

Chemotherapy for tuberculosis has been practiced in the Army on a small scale only, and then in an investigative manner in conformity with other current studies on chemotherapy in tuberculosis. Promine has been tried in a few cases of nonpulmonary tuberculosis. It is too early to make any statement with regard to its effect in controlling the disease. In the cases under observation no untoward results have occurred.

#### DISCHARGE AND VETERANS' CARE

The principal problem prior to discharge of a tuberculous patient from the Army is insurance that he is properly indoctrinated to continue his care

after he reaches a Veterans Administration facility, or to continue under periodic observation if his disease is considered arrested and no further medical measures are needed than occasional reëvaluation to determine if the lesion is stable.

It is a notorious fact that during and after the other world war a high percentage of patients eligible for veterans' care elected to forego such care,—and with disastrous results. Many patients whose lesions were in a minimal stage, relatively susceptible to treatment, left hospitals against advice and returned months later to die of advanced disease. Much has been written on this subject and various reasons for the unfortunate situation indicated. Chief among the reasons offered are those relating to compensation. It has been stated vigorously by many who have investigated the subject that the laws in effect encourage patients to select compensation at a high rate outside a hospital in preference to hospitalization with a low monetary compensation during treatment. In spite of special provision for men with families, this compensation differential apparently had the effect of inducing men to stay away from hospitals.

At present both the military services and the Veterans Administration are making every effort to indoctrinate tuberculous patients on the need for continued care. The attention of the latter is drawn forcibly to two reasons for not abandoning treatment, the patient's own welfare and the protection of those around him. Every soldier in the Army upon whom a diagnosis of tuberculosis or suspected tuberculosis is made is given a copy of a booklet, prepared with the coöperation of the National Tuberculosis Association, entitled "What You Should Know About Tuberculosis." This gives him information on the character of the disease and on the urgent need for continuing his medical care after discharge. Various special privileges in his postdischarge life are clearly indicated to him, including arrangements for his re-employment after he is restored to health.

Other measures carried out in Army hospitals include talks by ward officers and tuberculosis specialists, and the showing of motion pictures on tuberculosis. There is reason to believe that the desired indoctrination is increasingly effective. The problem is not a simple one, however, because of the fact, universally recognized, that after short periods of treatment and abatement of symptoms incident to the spread of disease patients commonly feel well. Under such circumstances it is not surprising that the urge to return to normal life is strong, and this urge is particularly vigorous after years of military discipline. This social problem demands continued effort in its solution.

#### SUMMARY

Tuberculosis has been a conspicuous problem in military medicine, as shown by the figures of all wars in which accurate statistics have been kept. Its gravity as a cause of disability in the United States Army in this war and the last has proved inversely proportional to the effectiveness of machinery for screening-out cases of tuberculosis at the time of acceptance for military

service, for most cases developing in service have represented failure to detect small lesions existing at the time of the initial physical examination.

Exclusion of tuberculosis from military service under current conditions is dependent on rapid, mass X-ray methods. Cases developing in the United States Army in the present war for the most part represent extension from small areas of infiltrative tuberculosis not previously detected. Extension from scarred and calcified primary lesions has not been demonstrated. Statistics suggesting an increasing amount of exogenous infection overseas have been reported in the Canadian Army, but indications are not yet at hand of a comparable situation in our Army. The total admission and discharge rates in our Army in this war are approximately one-tenth of those prevailing in World War I.

The predominant type of tuberculosis occurring in our Army is the chronic, ulcerative, pulmonary form. Acute forms are relatively rare, at least in the white race, and up to the present, while numerous advanced cases have been returned from overseas, indications are not evident that climate or any specific environment is a factor in the development of fulminating disease. Great progress has been made in evacuation of patients, particularly by air. All active tuberculosis is cause for discharge, but arrangements are in effect for preliminary treatment in the Army and indoctrination on the great importance of continuation of care after separation from the service and establishment of veteran's status.

#### SUMARIO

La tuberculosis ha constituido un problema importante en la medicina militar, como lo demuestran las cifras de todas las guerras en que se han mantenido estadísticas exactas. Su gravedad como causa de incapacidad en el Ejército de los Estados Unidos, tanto en esta guerra como en la pasada, se halla en razón inversa a la eficacia de la maquinaria utilizada para entresacar los casos de tuberculosis en el momento de la admisión para el servicio militar, ya que la mayoría de los que se han manifestado durante el servicio representaban la falta de identificación de pequeñas lesiones existentes al realizarse el primer examen físico.

La exclusión de la tuberculosis del servicio militar en las condiciones actuales depende del empleo de métodos rápidos de radiografías en masa. Los casos que se han presentado en el Ejército de los Estados Unidos durante la actual guerra representan en su mayoría la difusión desde pequeñas zonas de tuberculosis infiltrativa no descubiertas previamente. No se ha comprobado tal difusión cuando se trata de lesiones primarias cicatrizadas y calcificadas. Se han presentado estadísticas que indican un aumento de afecciones exógenas en el Ejército Canadiense en ultramar, pero no de cuenta con datos que muestren una situación parecida en el Ejército de Estados Unidos. Los coeficientes de admisiones y licenciamientos del Ejército de Estados Unidos en esta guerra vienen a representar aproximadamente la décima parte de los observados en la Primera Guerra Mundial.

El tipo predominante de tuberculosis en el Ejército de Estados Unidos es la forma crónica, ulcerativa, pulmonar. Las formas agudas son relativamente raras, por lo menos en la raza blanca, y hasta ahora, aunque han regresado de ultramar numerosos casos avanzados, no se ha comprobado que el clima o el ambiente constituyan un factor de peso en el desarrollo de la enfermedad fulminante. Se han alcanzado grandes adelantos en la evacuación de enfermos, especialmente por vía aérea. Toda tuberculosis activa constituye causa de licenciamiento, pero también se facilita tratamiento preliminar en el Ejército y se insiste en la gran importancia de continuar el cuidado de la enfermedad después de la separación del servicio y del establecimiento del estado de veterano.

# THORACOPLASTY<sup>1</sup>

## Report on 240 Consecutive Patients

PAUL D. CRIMM

This review is presented in an effort to evaluate the results of extrapleural thoracoplasty for pulmonary tuberculosis which was performed in this sanatorium. Ninety per cent of the patients admitted to this institution are either moderately or far advanced cases of tuberculosis, the majority with bilateral involvement. Therefore, this series consists of cases which are typical of those found in many sanatoria. No attempt is made, for the sake of statistics, to differentiate between "good chronics" and "bad chronics." A survey of three postoperative groups, which have been operated from one to ten years, is analyzed.

### ANALYSIS OF OPERATIONS

In this series, 458 operations were performed by the author on 240 consecutive patients, ages 16 to 66. Of these patients, 99, or 41.0 per cent, had moderately advanced and 141, or 59.0 per cent, far advanced pulmonary tuberculosis. The operative mortality per operation was 2.6 per cent. None of these patients had experienced sputum conversion by either bed-rest or other surgical procedures. Thoracoplasty was selected as the choice of operation because of cavitation, extent of the disease or the character of the lesions. This operation was performed on the lung with the most involvement, as evidenced by roentgenograms, in 156, or 65.0 per cent, of the 240 patients who had bilateral disease. Five of these patients received bilateral thoracoplasty. Generally, the lung with the least involvement was treated with bed-rest, in 6 cases with pneumothorax and with paraffin plumbage in 10.

Pneumothorax was either attempted, or considered futile, on the more involved side before surgery was performed. Ninety-five, or 40.0 per cent, of this series received pneumothorax for an average of eight months prior to thoracoplasty. Ninety-one patients had one-stage thoracoplasty, which consisted of the removal of three to five ribs; 102 had two stages, consisting of the removal of five to seven ribs; 32 had three stages, 10 four stages, 3 five and 2 six. One hundred and ninety-three patients, or 80.0 per cent, had partial thoracoplasty, consisting of one or two stages. Fifty-nine patients had anterior operations in conjunction with their posterior operation through a lateral or anterior approach.

Twenty-two patients had phrenic nerve operations on the operated side prior to thoracoplasty. Twenty-three of the 240 patients had paraffin plumbage, 13 of which were performed on the side of the thoracoplasty; 3 of these plombages were removed at the time of thoracoplasty, since they were lateral packs and did not prove satisfactory. Ten of the plombages were not removed and thoracoplasty was performed over the site of the pack, because of breakdown of lesions below the paraffin. Seventeen patients of the 240 had complications of

<sup>1</sup> From Boehne Tuberculosis Hospital, Evansville, Indiana.

tuberculous empyema, 11 of whom are deceased, while 5 are apparently arrested. However, demise of the 11 patients was not due to tuberculous empyema. One patient is still positive, due to disease in the opposite lung. Six of the 17 patients had a Schede operation. Ten patients of the 240 had tuberculous laryngitis of whom 5 are deceased and 5 are well and working.

We have classified this series into three postoperative groups, dependent upon the length of time since their operations. Group I reports the course of the 108 cases which were operated eight to ten years ago. This is the largest group because of the fact that no surgery had been performed previously in this institution and a great many "chronics" were waiting for an operation to be performed.

Group II analyzes 67 patients who were operated five to seven years ago. Group III surveys 65 cases operated one to four years ago. These groups are subdivided into those who had positive sputum, those who had negative sputum, those who are arrested, well and working, those who have died of tuberculosis and those deceased from other causes. The total patient mortality of each group is subdivided into operative mortality per patient and nonoperative deaths.

#### POSTOPERATIVE GROUP RESULTS

Group I (chart 1) consists of 108 patients who have been operated from eight to ten years ago. Sixty-eight per cent have a negative sputum and, of these 65 per cent are arrested, well and working; the remaining 3.0 per cent are on limited activity. Five per cent still have a positive sputum. The total patient mortality is 27.0 per cent. The nonoperative mortality rate is 26.0 per cent. Eighteen per cent died of tuberculosis, while 8.0 per cent died from other causes. The operative mortality per patient was 1.0 per cent. Bacillary content of pulmonary secretion was determined either by a concentration method or by gastric lavage examinations. (Most of the third postoperative group had at least one gastric lavage. At the present time all thoracoplasty patients have five gastric washings over a six months' period. This is the most accurate method of obtaining specimens for study. In this series cultures were not made.)

Group II (chart 1) consists of 67 cases who have been operated from five to seven years ago. Fifty-four per cent have a negative sputum and, of these, 44.0 per cent are arrested, well and working; the remaining 10.0 per cent are on limited activity. Ten per cent still have a positive sputum. The total mortality is 26.0 per cent. The nonoperative mortality is 16.0 per cent. Twenty per cent died of tuberculosis, while 6.0 per cent died from other causes. The operative mortality per patient was 10.0 per cent. There were more poor surgical risks in this group, as shown by comparing the operative mortality rates. Although 10.0 per cent still have a positive sputum at this time, they show marked improvement because of their operations.

Group III (chart 1) consists of 65 cases who have been operated from one to four years ago. Sixty-six per cent have a negative sputum and 48.0 per cent of these are arrested, well and working. Since this group of patients has been operated more recently, 18.0 per cent are yet on limited activity, while 22.0

per cent have a positive sputum. Both of these percentages will decrease as the postoperative period increases. The total mortality of this recent group is 12.0 per cent. The operative mortality per patient is 6.0 per cent. The nonoperative mortality is 6.0 per cent, 3.0 per cent dying from other causes, while 3.0 per cent have died of tuberculosis, as compared with 18.0 and 20.0 per cent in the other groups. Conversely, this percentage will increase in direct

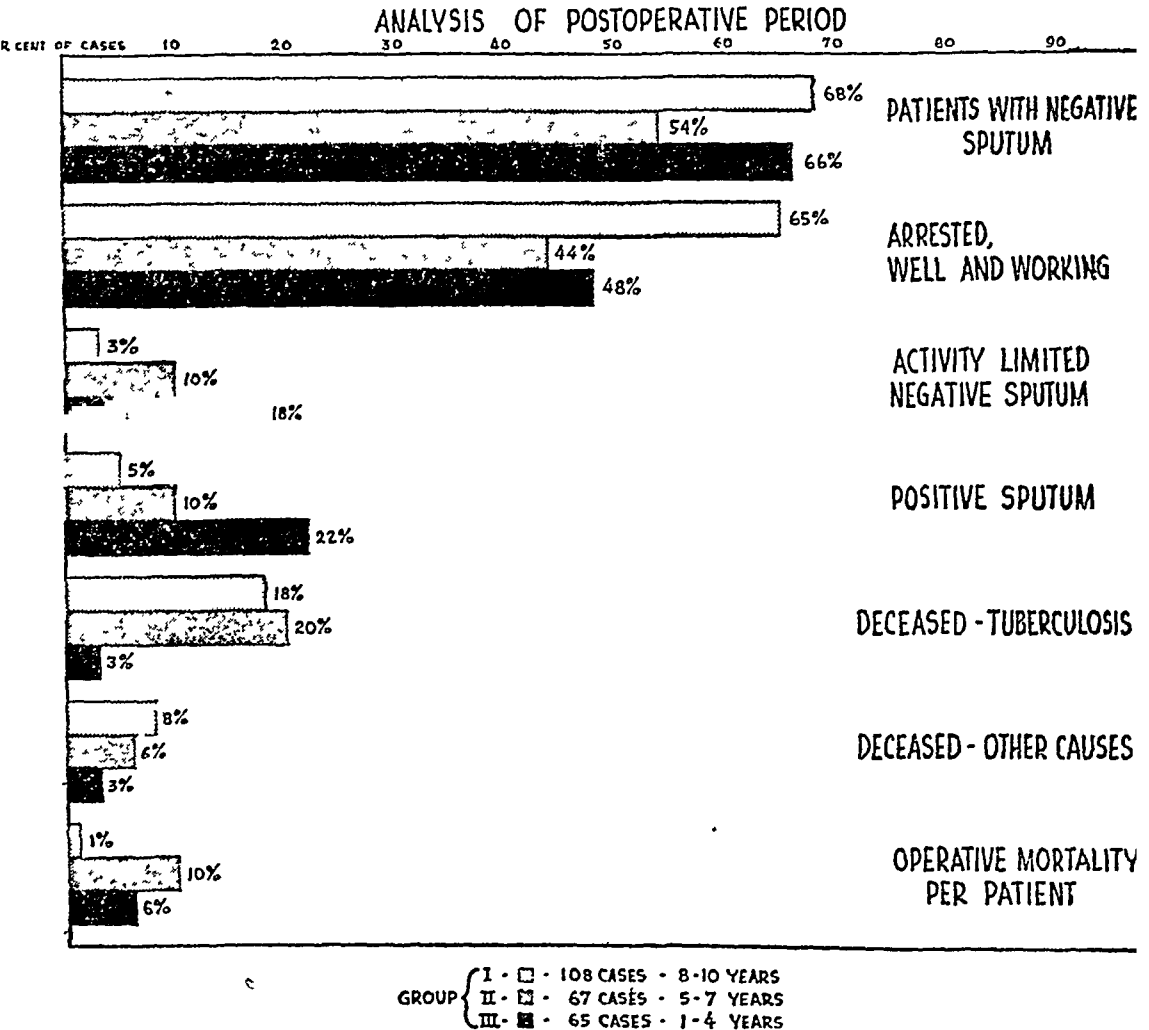


CHART 1

proportion to the postoperative period. In most of these patients who died of tuberculosis, death was caused by a flare-up of the old lesions in the opposite lung. The life of several patients could have been saved had they consulted a chest specialist as soon as the disease became reactivated. The operative mortality per patient was 6.0 per cent, as compared to 10.0 per cent in group II and 1.0 per cent in group I. This may point to the fact that the longer we wait to do thoracoplasty on border-line cases, the less will be the operative mortality. This



applies especially to the disease in the contralateral lung, in which lung it was arrested longer in the patients in group I.

In summarizing the three postoperative groups of 240 patients (chart 2), 63.0 per cent have a negative sputum, of whom 54.0 per cent are arrested, well and working, while 9.0 per cent are on limited activity, although their sputum is negative. Eleven per cent still have a positive sputum; however, all but 4 of these patients are markedly improved. A few need further operation. There

SUMMARY OF GROUPS I, II AND III - 240 CASES

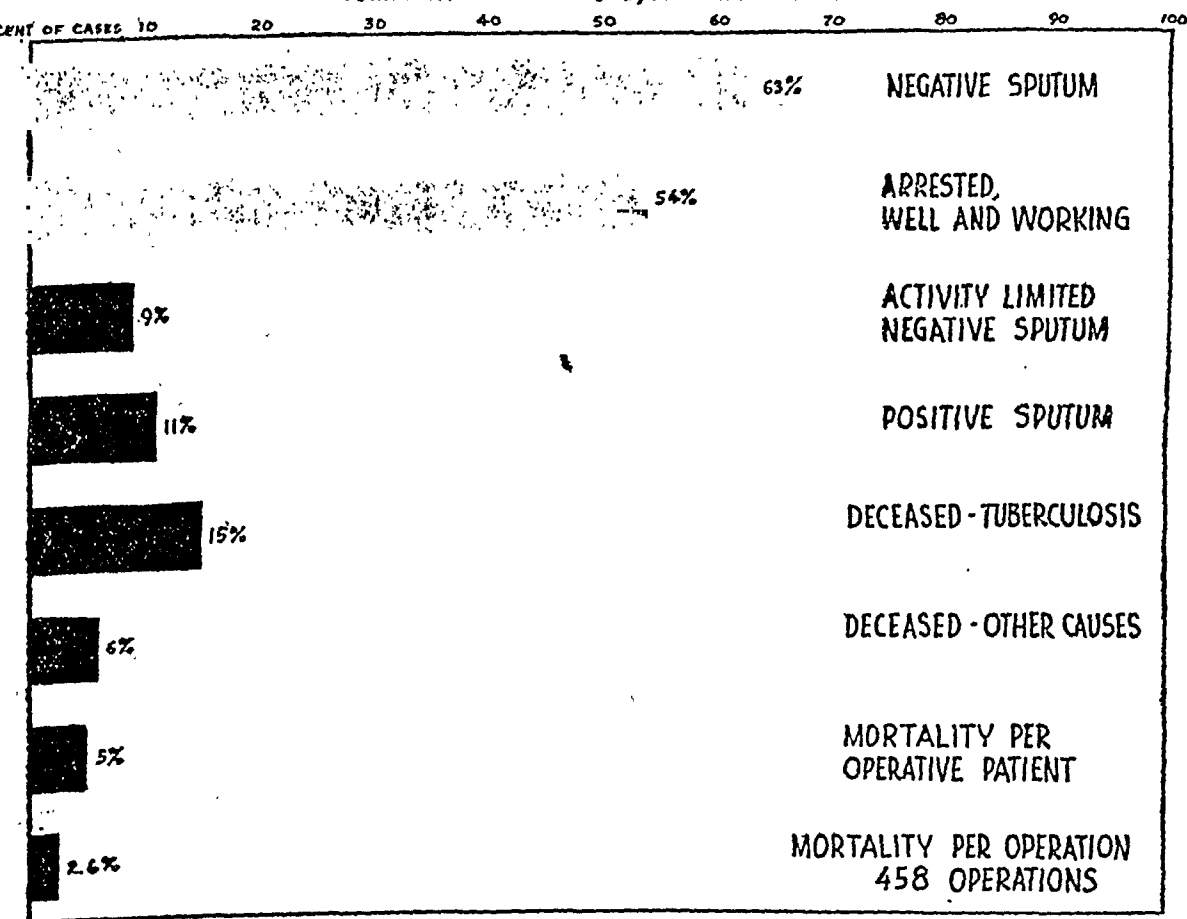


CHART 2

is no doubt that some of these patients who have positive sputum would have obtained a negative one by now, had complete thoracoplasty been performed in the beginning. An effort was made to conserve their respiratory reserve with a limited amount of surgery. A revision operation performed when the patient is a good operative risk will generally conserve vital capacity, much more so than a complete thoracoplasty performed when the patient is not such a good surgical risk. Moreover, a sufficient period of time has elapsed to further heal the disease in the opposite lung, which is advantageous.

The total mortality rate of the entire series to date is 26.0 per cent. The

cause of death in 15.0 per cent, or 35 patients, was attributed to tuberculosis, and 6.0 per cent (15 patients) died from other causes, namely: chronic nephritis, one; nephrosis, one; uremia, one; pneumonia, 4; brain abscess, one; heart disease, three; typhoid, one; suicide, 2 and intestinal obstruction, one. Twenty-nine of the 35 patients dying of tuberculosis lived from two to nine years following surgery. The average span of life was three and one-half years.

In considering postoperative mortality per operation, all patients who died within two months after thoracoplasty (1) were considered in this category which was 2.6 per cent. The mortality per operative patient was 5.0 per cent. All of these patients were autopsied. Two patients died from cerebral embolism following the first month of surgery, one from pulmonary embolism two months after surgery and 6 of cardiac failure within the first postoperative week (2 of the 6 had fatty degeneration of the liver). One died of tuberculous meningitis eleven days later, and one died from spontaneous pneumothorax in the opposite side five days after surgery. One patient died of acute pericarditis ten days after operation.

#### OPERATIVE DETAILS

The operative time for this series averaged forty-five minutes for the first stage and a shorter time for the following stages. For the most part, nitrous oxide and ether were employed for anesthesia. Patients with considerable amount of sputum were operated later in the day, in order to facilitate a more thorough emptying of the cavity. Several patients were bronchoscoped immediately after operation which aided their immediate and late recovery. The modern posterolateral operation, universally accepted, was used. Semb's apicolysis and partial scapulectomy aided the collapse in a few cases. The number and length of ribs removed at any one time was dependent upon the medical and surgical estimation of how much the patient could stand, as well as the condition of the patient before and during the operation. As a general rule, meticulous hemostasis was ignored and not more than one or two blood vessels were tied during an entire operation. Hemostats were permitted to remain until the operative wound was ready for closure. Cautery was used occasionally for hemostasis around the transverse spinous processes. The less catgut used and the less constriction of blood supply, the faster the tissue heals. Continuous sutures of chromic, plain and silk were used to close muscle, fascia and skin, respectively. Continuous sutures speed up the operation.

Wherever possible the transverse processes were left intact, commensurate with the size and location of the cavitation, in order to avoid scoliosis of the spine. (One patient who had a scoliosis of the spine had a revision operation and in denuding a small piece of regenerated rib the spinal canal was entered. A catheter drain was left beneath the scapula and the patient drained spinal fluid from ten days to two weeks. At that time the opening sealed over and the patient made an uneventful recovery, with the exception of a headache and slight temperature.)

Postoperative care is most important to the patient who has had a thoraco-

plasty for tuberculosis. Few patients in this series suffered surgical shock. Seldom was a blood transfusion necessary, although 5 per cent glucose and saline were routinely given intravenously following operation. Patients were placed routinely in an oxygen tent, on their operated side, immediately after surgery. Suction was used to remove any excessive sputum. A drain was placed in a great many wounds for forty-eight hours, especially if there was considerable ooze. (We have found that wound fluid is increased by the use of sulpha powder. Graham (2) states, "One advantage in providing drainage of the wound is that, if hemorrhage should occur blood will run out and be detected.") In some cases a wound did not close by first intention if the blood supply was inadequate. All patients were kept on bed-rest for six months following their last stage operation. A few privileges were allowed during the last two months.

#### COMMENT

Every patient should be advised that a thoracoplasty is just an aid in the cure of pulmonary tuberculosis. In turn, every patient should be given a satisfactory period of bed-rest before minor or major surgical intervention. A few cases, such as hemorrhaging patients, may demand immediate collapse therapy of some kind. In this series, thoracoplasty was employed only in cases with chronic disease and where cavitation was present. The extent of this irreversible operation always bordered on the side of not enough ribs removed, rather than too many ribs, in order to preserve an adequate respiratory function for the patient with a chest reconstructed by thoracoplasty. Vital capacity was not sacrificed for sputum conversion, because several patients have lived comfortably for a long time with a positive sputum. In this series, only 5 patients had bilateral thoracoplasty, while 10 had paraffin plombage in the opposite lung. This conserves vital capacity to a greater extent than does a bilateral thoracoplasty.

The function of both diaphragms should be maintained for the benefit of the patient's future comfort. In this series, the phrenic nerve was crushed occasionally, but seldom interrupted. Only 22 patients in the entire series had phrenic nerve operations and some of these could have been omitted, with the exception of those who had cavitation in the lower lobe. In one patient, phrenic nerve interruption interfered with the position and at times the function of the stomach. Cournand and Richards (3) state that, "Phrenicectomy appears regularly to disturb pulmonary function to a considerable extent." Best and Taylor (4) assert that "6.0 per cent of the total amount of air breathed during deep respiration is accounted for by the action of the diaphragm." Pinner *et al.* (5) state that "thoracoplasty lungs, if not complicated by diaphragmatic paralysis, participate to a considerable degree in respiration." Wright and Woodruff (6) state that "limitation of motion on part of thoracic cage and the diaphragm accounts for most of respiratory damage we see." Personally, the author feels that the functioning of both diaphragms gives the surgeon a degree of confidence in the respiratory reserve of thoracoplasty patients, in the absence of bronchspirometric analyses. Two patients in this series had tuberculous

tracheobronchitis. One died several months after thoracoplasty and one treated with ultraviolet radiation (7) recovered. In regard to the operation of choice for patients with tuberculous tracheobronchitis, Alexander *et al.* (8) believe that "thoracoplasty is the better operation, because the mortality is much lower and the percentage of apparent healing of tuberculosis is much higher over pneumonectomy for cases complicated by stenotic tuberculous bronchitis."

#### COMPARATIVE RESULTS OF OTHER SURGEONS

In 1937, Urquhart (9) reported 200 patients operated by thoracoplasty, with 59.5 per cent arrested. Freedlander and Wolpaw (10), 1937, reported 85 patients operated from 1932 to 1934 inclusive. Cavity closure and negative sputa were obtained in 57.0 per cent. Dolley *et al.* (11), 1939, reviewed 1,636 cases operated in different clinics, and reported that 43.0 per cent were able to work after surgical collapse. O'Brien *et al.* (12), 1940, reported that in 511 patients 61.65 per cent had sputum conversion. Miller, Schaffner and Hiltz (13), 1940, reported 49.0 per cent arrested after operating 100 patients during 1934 to 1938 inclusive.

Overholt (14), 1941, reported on a questionnaire sent out to 874 patients; 293 answered the questionnaire and it was found that 83.0 per cent of this number had been working on an average of twenty-three months.

Adams and Dufault (15), 1941, reported 65.2 per cent cured of 241 patients over a sixteen-year period. Skinner *et al.* (16) in the same year reported 71.0 per cent cured of 226 patients over a period of sixteen years. Dieffenbach and Crecca (17), 1941, reported 100 patients, of whom 71.7 per cent were arrested over a two-year period. Finney (18), 1941, reported 62.5 per cent arrested of 104 cases over an eight-year period. Meltzer (19), 1941, reported 181 patients, of whom 66.0 per cent were arrested and 50.4 per cent able to work. Vineberg *et al.* (20) reported 100 patients in 1941; 42.5 per cent of 47 bilateral cases were well and working following thoracoplasty. Aufses (21) reported 90 patients who were operated over a five-year period; of the total, 71.0 per cent were arrested. Harrison and Berry (22), 1943, reported on 150 cases, with 74.7 per cent cavity closure after a brief postoperative period.

It is obvious that the classifications in the cited references are not identical; therefore, we have correlated the figures as follows: all those cases definitely reported as either arrested, well and working make up one group, while those with sputum conversion and cavity closure make up the second group. Both groups have negative sputum, but the latter group of patients are as yet not able to work. In the 10 reports of others regarding thoracoplasty results, an average of 58.5 per cent of those operated have a negative sputum and are arrested, well and working. In the remaining 4 reports on negative sputum and cavity closure, 64.6 per cent of the patients had sputum conversion, but were not reported as being well enough to work. In our series of 240 patients, 63.0 per cent have negative sputum; of these, 54.0 per cent are arrested, well and working and the remaining 9.0 per cent are on limited activity.

## SUMMARY

1. Four hundred and fifty-eight thoracoplasties were performed on 240 consecutive patients, ages 16 to 66. Of these patients, 99, or 41.0 per cent, had moderately advanced and 141, or 59.0 per cent, far advanced pulmonary tuberculosis. The operative mortality per operation was 2.6 per cent.

2. All patients were operated over a period of one to ten years. An analysis of three postoperative groups is made; those patients who were operated eight to ten years ago, those operated five to seven years, and those one to four years.

3. Of the 240 patients, the total mortality to date is 26.0 per cent. The nonoperative mortality was 21.0 per cent—15.0 per cent died of tuberculosis and 6.0 per cent from other causes. The operative mortality per patient was 5.0 per cent.

4. Of the 240 patients, 63.0 per cent have a negative sputum, while 11.0 per cent are positive. Of the 63.0 per cent with a negative sputum, 54.0 per cent are arrested, well and working, while 9.0 per cent are on limited activity.

5. A few operative details are mentioned, various operative procedures are discussed and the comparative results of other thoracic surgeons are reported.

## SUMARIO

1. Efectuáronse 458 toracoplastias en 240 enfermos consecutivos de 16 a 66 años de edad. De estos enfermos, 99 (41.0%) padecían de tuberculosis pulmonar moderadamente avanzada y 141 (59.0) muy avanzada. La mortalidad operatoria representó 26 por cien operaciones.

2. Todos los enfermos fueron operados durante un período de 1 a 10 años. Se presentan análisis de tres grupos por separado: de los enfermos operados hace 8 a 10 años, los operados hace 5 a 7 años, y los operados hace 1 a 4 años.

3. La mortalidad total hasta ahora representa 26.0%. La mortalidad no operatoria representó 21.0%: 15.0% por tuberculosis y 6.0% por otras causas. La mortalidad operatoria representó 5 por cien enfermos.

4. De los 240 enfermos 63.0% tienen esputo negativo, y 11.0% positivo. Del 63.0% de esputo negativo 54.0% están estacionados, bien y trabajando, mientras que 9.0% disfrutan de actividad limitada.

5. Menciónanse algunos detalles operatorios, discútnense varias técnicas y compáranse los resultados obtenidos por otros cirujanos.

Grateful acknowledgment and thanks are due Clara T. Kruse, B.S., M.T., of Boehne Hospital Laboratory for her valuable assistance.

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## CONVERSION OF PULMONARY SECRETIONS FOLLOWING COLLAPSE THERAPY<sup>1</sup>

JOHN D. STEELE

Following collapse therapy for pulmonary tuberculosis it is often difficult to determine whether or not the disease is active. Roentgenograms taken prior to and following the collapse procedure are not comparable and often the postoperative films are of little value in determining the activity of the collapsed lesions. Following a thoracoplasty, for instance, a roentgenogram showing an opacity at the site of the original lesion with an absence of any areas or suspicious areas of cavitation is usually considered to be a satisfactory technical result. However, even though such an appearance is attained soon after completion of the thoracoplasty and persists in subsequent films, we realize that the relaxation produced by the thoracoplasty has not immediately healed the original lesion but has merely placed it in a situation which will favor healing. The time required for healing, provided the lesion does heal, will depend on a considerable number of factors, including the patient's resistance, the amount of fibrosis already present in the lesion prior to thoracoplasty, etc. Since we can expect no further information from the roentgenogram as to the activity of the disease, we must, therefore, use other methods of examination to gauge activity. If accurate, repeated examinations of pulmonary secretions show the presence of tubercle bacilli following collapse therapy, we feel that we must conclude that the lesion is still active and that, later on, failure to detect tubercle bacilli may indicate inactivity.

In an attempt to determine how long pulmonary secretions can reasonably be expected to remain positive following adequate surgical relaxation of pulmonary tuberculosis, the records of 142 patients whose operations had been completed between November, 1938 and November, 1943 were reviewed. One hundred and six of these had unilateral thoracoplasties; one had a bilateral thoracoplasty; 28 had unilateral extrapleural pneumonolyses followed by paraffin fillings; 3 had bilateral paraffin fillings; and 4 had thoracoplasties with contralateral paraffin fillings. The technique used in the performance of both of these operative procedures was that described by Alexander (1). We consider that the desired effect of both thoracoplasty and extrapleural pneumonolysis is the production of a relaxation of the diseased portion of a lung.<sup>2</sup>

Since we were primarily interested in the problem of the conversion of pulmonary secretions following collapse therapy, it was necessary to discard those cases having factors which might confuse the issue, such as an active or questionably active contralateral lesion, tuberculous bronchitis, etc. It was thus necessary to discard, for the purposes of this review, the records of all but 57 patients who

<sup>1</sup> From the Departments of Surgery, Mairdale Sanatorium, Wauwatosa, Wisconsin, and the Marquette University School of Medicine, Milwaukee, Wisconsin.

<sup>2</sup> When an extrapleural pneumonolysis is performed, a relaxation of the diseased area is produced, and the relaxation is maintained by filling the extrapleural space with paraffin.

had lesions which were presumably active on one side only and whose roentgenograms revealed a satisfactory technical result soon after completion of the operative procedure. Of these 57, thoracoplasty was performed in 43; extrapleural pneumonolysis followed by paraffin filling in 14. The reasons for non-inclusion of the remaining 85 cases were as follows:

Bilateral disease.....	29
Not followed (discharged against medical advice).....	17
Tuberculous bronchitis.....	11
Unclosed cavities.....	11
Empyema.....	6
Bronchiectasis (possibly tuberculous).....	3
Gastric contents negative on culture prior to operation.....	3
Gastric contents not cultured following operation (sputa negative on culture).....	3
Monaldi cavity drainage prior to thoracoplasty.....	1
Died of right heart failure one and one-half years following thoracoplasty— sputum remained positive.....	1

During the period of observation it was our custom to have sputum specimens examined postoperatively at intervals not exceeding three months. In most instances, 3 consecutive forty-eight-hour specimens were collected; if negative on smear and concentrate, all specimens were cultured. If a patient denied raising sputum or if sputum cultures were negative, the gastric contents were then cultured. The laboratory technique used in examining the specimens of the sputa and gastric contents of our patients has been described by Anderson (2).

Of the 57 cases selected for review, 54 are negative on culture of their gastric contents as well as on culture of their sputa (if any). The status of the 3 patients whose secretions remain positive will be noted later.<sup>3</sup> The number of gastric aspirations performed on these 54 patients varied from 2 to 9, averaging 4.01 per patient.

In an attempt to ascertain whether or not the type of disease present preoperatively had any relation to the rate of conversion of the pulmonary secretions postoperatively, the preoperative roentgenological appearance of the lesions of the 54 negative patients was classified as predominantly exudative, mixed or predominantly productive (all patients were Caucasian, except one who was a Mexican Indian). An attempt was also made to correlate the rapidity of conversion of the pulmonary secretions with the source and method of laboratory examination necessary to demonstrate the tubercle bacilli prior to operation. In presenting the following statistics only the most significant figures have been included with the hope of minimizing the confusion which often attends such statistical presentations.

Of 5 patients whose lesions were classified as exudative preceding collapse therapy, 3 remained positive on sputum culture for twelve, thirteen and sixteen months, respectively; one produced no sputum following completion of her thoracoplasty but remained positive on culture of her gastric contents for seven

<sup>3</sup> Of the 68 followed patients who were not included in this review, 27 have negative cultures of their gastric contents and 9 are negative on sputum culture. Thus, the sputa or gastric contents of 36 of the 125 followed patients remain positive.



months; the remaining patient was positive on sputum culture for one month only following completion of the operation.

Of the 34 patients whose lesions were classified as mixed before collapse therapy, the sputa of 9 patients were negative on culture within one month, and the sputa of 4 patients were negative on culture within three months of the completion of the operations. The sputa of 10 patients remained positive on culture from one to six months; the sputa of 3 patients remained positive on culture from six to twelve months; the sputum of one patient was positive on culture fifteen months following completion of her thoracoplasty.

Of the 15 patients whose lesions were classified as predominantly productive in type prior to collapse therapy, the sputa of 7 patients were negative on culture within three months. The sputum of one patient and the gastric contents of another remained positive on culture at twelve months. One patient had a positive sputum concentrate at three months, a positive sputum culture at eight months and a positive culture of his gastric contents at fifteen months.

Although the number of cases is probably too small to be significant, it would appear, as might be expected, that our patients having predominantly exudative lesions prior to collapse therapy tended to require more time for conversion of their secretions than the other groups. However, a number of patients in both the mixed and productive groups remained positive on culture of their sputa or gastric contents for a year or more. The sputa of a higher percentage of patients in the productive group became negative on culture within one month of completion of the operations than in the mixed group.

An attempt was made to correlate the rapidity of conversion of pulmonary secretions with the source of positive secretions prior to collapse therapy and with the laboratory procedure necessary to demonstrate tubercle bacilli in these secretions. Of 37 patients who had positive sputum smears or concentrates prior to therapy, 10 became negative on sputum culture within three months. Of 16 patients who were positive on sputum culture only prior to therapy, 11 became negative on sputum culture within three months, although 2 others remained positive at six and eight months, respectively. Of the 11 patients who were positive "only" on culture of their gastric contents prior to therapy, the cultures of 4 became negative within three months but 2 others remained positive at eight months and one other at one year. One patient who had a positive culture of her gastric contents preoperatively remained positive on sputum culture for fifteen months postoperatively.

Thus, it would appear that the rate of conversion of pulmonary secretions had no significant relation to the source of secretions prior to collapse therapy, since several patients who were positive "only" on examination of their gastric contents before operation remained positive for a year or more afterward. It is likewise doubtful whether the ease of demonstrating tubercle bacilli in pulmonary secretions preoperatively is of any significance in relation to the rate of conversion.

In reviewing this series of cases it was constantly observed that the status of pulmonary tuberculosis cannot be evaluated accurately by the examination of

concentrated sputa alone or by the disappearance of sputum. Two of our patients who denied raising sputum following therapy were found to have positive gastric contents at seven and ten months, respectively. Six patients who had persistently negative concentrated sputum specimens immediately following operation remained positive on sputum culture from six to fifteen months.

It was also observed that it was possible to obtain negative cultures of the gastric contents in a large majority of patients following major collapse therapy procedures within a reasonable length of time (two years or less). This finding had previously been observed by Furlong and Warren (3).

Of our 57 apparently uncomplicated unilateral cases, it has been mentioned above that 3 remain positive in spite of apparent satisfactory collapse according to the roentgenological appearance of their lesions (including films taken with a Potter-Bucky diaphragm). The status of these 3 patients is as follows: 2 patients who had predominantly exudative lesions prior to thoracoplasty remain positive on culture of their gastric contents at fourteen and fifteen months, respectively, following completion of their operations. The remaining patient was classified as having a mixed lesion preoperatively; she remains positive on sputum culture fifteen months after operation. It seems probable that the pulmonary secretions of these 3 patients will eventually be converted.

#### SUMMARY AND CONCLUSIONS

1. In an attempt to determine how long pulmonary secretions can reasonably be expected to remain positive following the adequate surgical relaxation of pulmonary tuberculosis, a series of apparently uncomplicated unilateral cases was reviewed.

2. It was found that cultures of the pulmonary secretions (sputum and gastric contents) of many patients remained positive for varying periods up to nearly two years but later became negative on culture.

3. Conversion of pulmonary secretions required longer in most patients having collapse therapy for predominantly exudative lesions.

4. The source of positive secretions (sputum versus gastric contents) prior to collapse therapy had no apparent relation to the rate of conversion.

5. The laboratory procedure (smear, concentrate or culture) necessary to demonstrate tubercle bacilli prior to collapse therapy had no apparent relation to the rate of conversion.

6. The gastric contents of a large majority of patients having major collapse procedures for unilateral lesions were found to be negative on culture within two years of completion of their operations.

#### SUMARIO Y CONCLUSIONES

1. Tratando de determinar por cuanto tiempo puede, lógicamente, esperarse que las secreciones pulmonares continúen siendo positivas después de una adecuada dilatación quirúrgica del pulmón tuberculoso, se estudió una serie de casos unilaterales sin complicaciones aparentes.

2. Los cultivos de las secreciones pulmonares (esputo y contenido gástrico)

de muchos enfermos, continuaron positivos por períodos variables y hasta casi dos años, pero luego se volvieron negativos.

3. La negativación de las secreciones pulmonares exigió más tiempo en la mayor parte de los enfermos en que se había ejecutado la colapsoterapia por lesiones predominantemente exudativas.

4. La procedencia de las secreciones positivas (esputo o contenido gástrico) antes de la colapsoterapia, no guardó relación aparente con la velocidad de la conversión.

5. El procedimiento de laboratorio (frote, concentración o cultivo) que fué necesario utilizar para encontrar los bacilos tuberculosos antes de la colapsoterapia, no guardó relación aparente alguna con la velocidad de la conversión.

6. El contenido gástrico de la gran mayoría de los enfermos en que se ejecutaron procedimientos de colapso mayor por lesiones unilaterales, mostró cultivos negativos en un término de dos años después de completarse la operación.

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# BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS<sup>1</sup>

## IV. A Geographical Adventure

### Part 2

B. A. DORMER, J. FRIEDLANDER AND F. J. WILES

#### *Group II. Cases of Mixed Exudative and Productive Disease*

*Case 9:* C.306, Indian male, aged thirty-two. In June, 1941 he complained of lassitude. In August, 1941 he began to cough and bring up sputum and consulted a doctor in February, 1942 who advised X-ray examination and pulmonary tuberculosis was diagnosed. He is a thin healthy looking Indian male. His temperature and pulse are normal. Sputum contains tubercle bacilli. Physical signs are bronchial breathing and a few crepitations at the upper lobes of both lungs.

An X-ray film (figure 13) shows scattered infiltration in the right upper lobe with possible cavitation and scattered infiltrations in the left upper lobe, possibly with cavities.

A bronchogram (right) (figure 14) shows bronchiectasis with cavitation in the right upper lobe and bronchiectasis of the middle lobe.

A bronchogram (left) (figure 15) shows bronchiectasis with cavitation in the left upper lobe (patient lying). Films taken with the patient standing showed numerous fluid levels in the left upper lobe (figure 16).

This case is a particularly good example of bronchographic geography. No amount of consideration of the history, the physical signs, and the conventional X-ray films would have led one to draw the picture shown in the bronchogram.

*Case 10:* C.329, colored male, aged forty-two. History is difficult to elicit owing to patient's dysarthria and inability to read or write. As far as can be ascertained he had an hemoptysis in 1939 and a cough for some time preceding this. He was admitted because of recent hemoptysis. He is a thin, ill looking colored male. His temperature is 98 to 99.6°F. Pulse 110. Sputum contains tubercle bacilli. Physical signs are crepitations over the whole of the right lung in front and at the back. Bronchial breath sounds are present at the left upper lobe with crepitations at the inferior angle of the scapula.

An X-ray film showed scattered fine infiltrations over the whole of the right lung suggestive of silicosis. There was a cavity 1½" x 2" in the right infraclavicular region at the periphery. Cavity or cavities were present at the right midzone. Left lung had a fine mottling throughout suggestive of silicotic lesions.

A bronchogram (figure 17) of the right lung shows the cavities clearly but there is a superadded bronchiectasis of the right upper lobe and no alveolar pattern.

#### *Group III. Cases of Mainly Productive Disease*

*Case 11:* E.232, European male, aged twenty-four. He began coughing in 1933 and brought up sputum. He was admitted to hospital where a right artificial pneumothorax was done in 1934 and refills were continued for eighteen months. In July, 1936 he began to cough again and was readmitted to hospital for six months. He felt well until 1938 when he had another six months in hospital. Last admission was on October 17, 1940,

<sup>1</sup> From the King George V Hospital for Tuberculosis, Durban, South Africa.

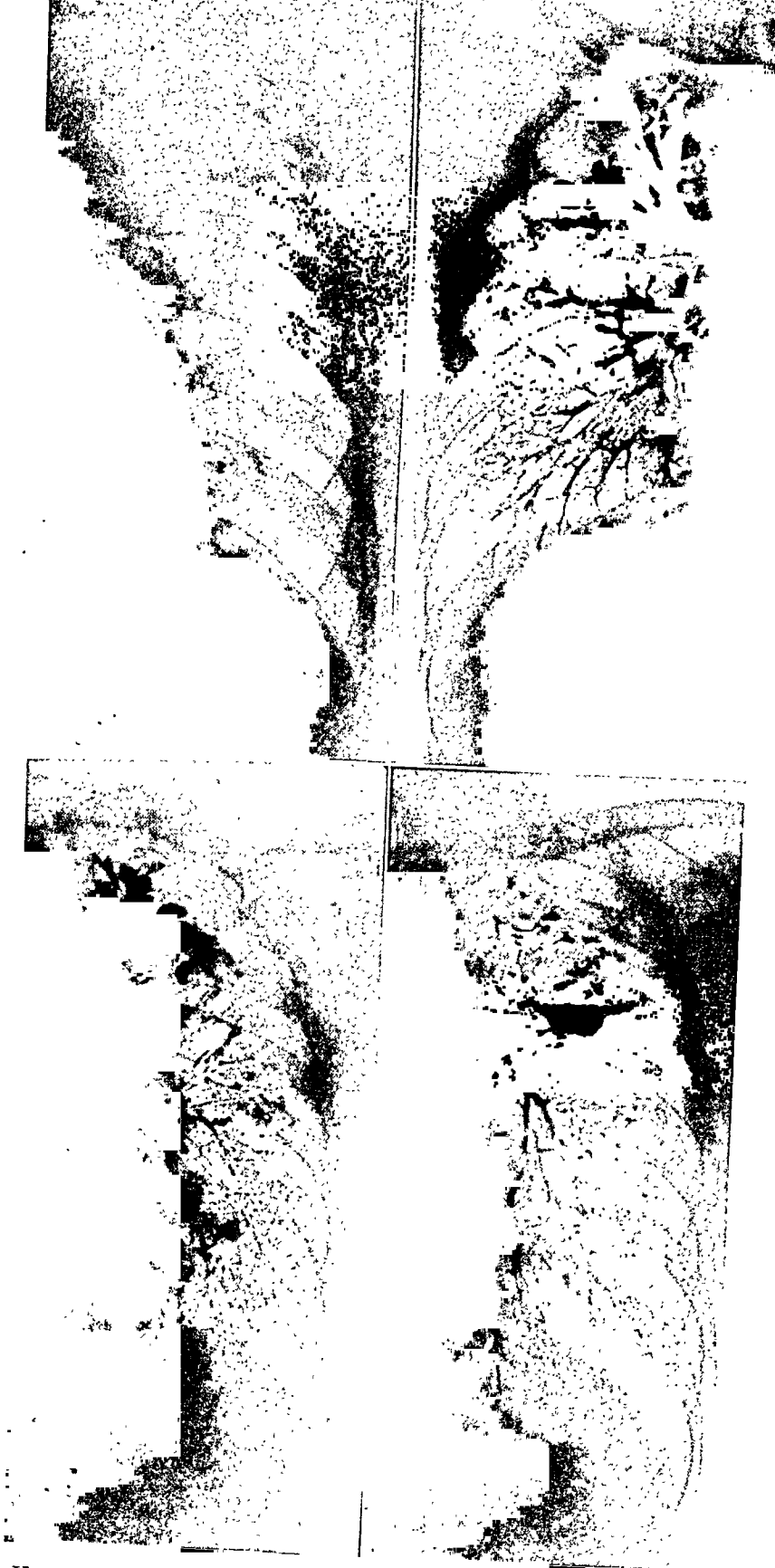


FIG. 13. Upper left; FIG. 14. Upper right; FIG. 15. Lower left; FIG. 16. Lower right

for cough and "feeling run down." He is a fit looking man with normal temperature and pulse. Sputum contains tubercle bacilli and has been positive since 1933. Physical signs are moderate wasting of right apex and increased vocal resonance over this area.

An X-ray film (figure 18) shows old-standing disease of the right upper lobe with retraction of the lobe and probable cavity; the costophrenic angle is obscured.

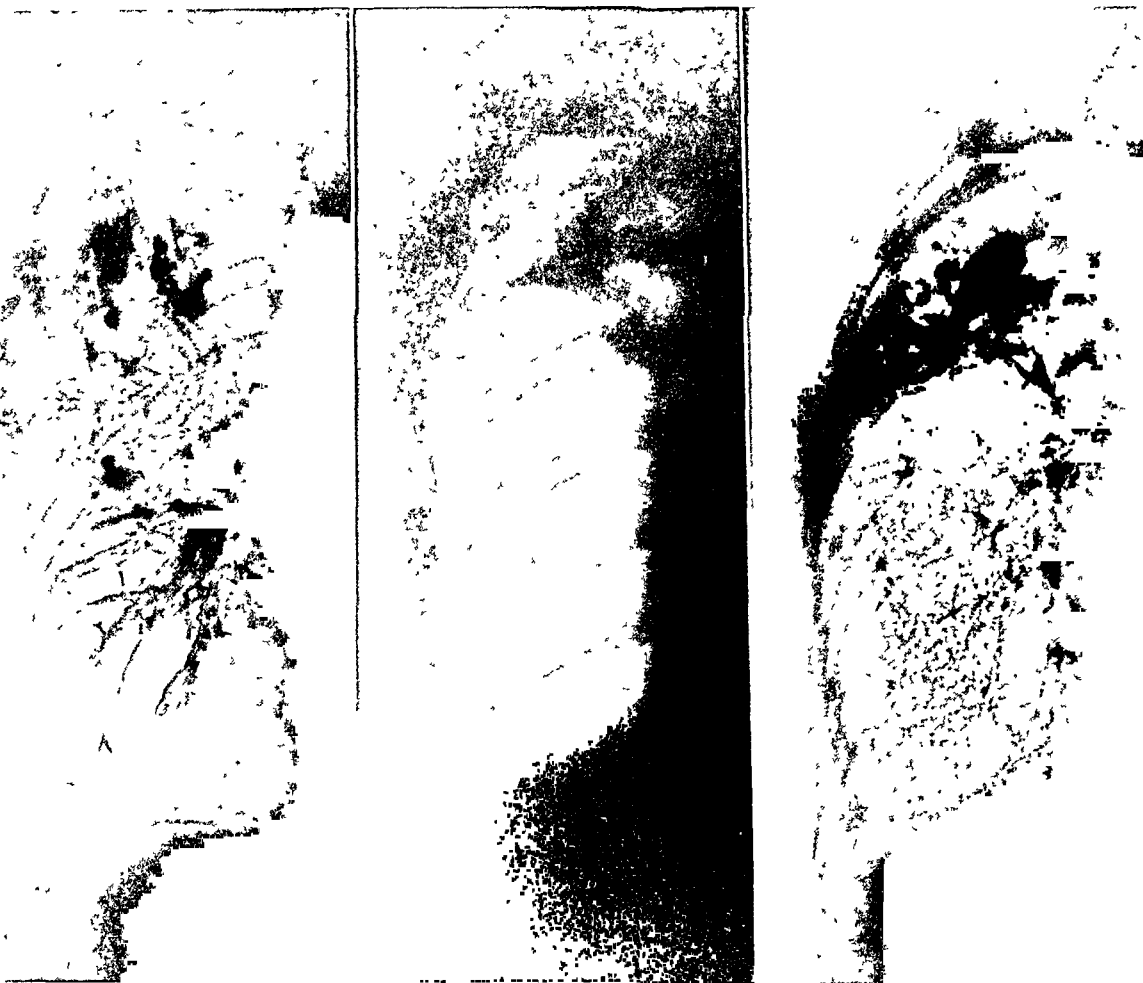


FIG. 17. Left; FIG. 18. Centre; FIG. 19. Right

A bronchogram of the right (figure 19) gives a clear map of the atelectatic upper lobe with its bronchiectasis and cavitation. The remainder of the bronchial tree is normal. There is marked deviation of the trachea.

*Case 12:* E.370, European male, aged thirty-six. Fourteen months ago he had a small hemoptysis. Two months later he developed a bad cough and was in hospital in Japan for a few weeks. Five months ago his cough was again troublesome and he was sent to hospital in Lourenco Marques. He was admitted to King George V Hospital on October 2, 1941, complaining of cough. He is a very healthy looking, well nourished merchant seaman. His temperature and pulse are normal. Sputum contains tubercle bacilli.

Physical signs are crepitations at both upper lobes with increased vocal resonance and whispering pectoriloquy at the right apex.

An X-ray film (figure 20) shows old-standing disease of both upper lobes with peaking of the left diaphragm.

A bronchogram of the right lung (figure 21) shows an atelectatic right upper lobe with greatly thickened pleura and the seat of bronchiectasis. The trachea is deviated to the right. The rest of the bronchial tree is normal.

The bronchial map in this case depicts the true disease with clarity.

*Case 13:* E.649, European male, aged twenty-eight. In April, 1941 he had hemoptysis but was never ill before. He is a healthy looking, well nourished European male. His temperature and pulse are normal. Sputum contains tubercle bacilli. Physical signs are a few crepitations in the right upper lobe at the back.

A roentgenogram (figure 22) shows vague mottling in both upper lobes.

Bronchogram of the right (figure 23) shows well defined atelectasis in the right upper lobe with bronchiectasis. Similar bronchiectases were found in the left upper lobe, with crowded bronchi.

In this case a careful consideration of the history, physical signs and conventional X-ray films would never have revealed the true condition made clear by bronchography.

*Case 14:* E.64, European male, aged forty-four. Following a routine examination for employment in a dairy he was told he had tuberculosis. He had a morning cough with a little sputum for years, but has never felt ill. He is a fit looking European male. His temperature and pulse are normal. Sputum contains tubercle bacilli. Physical signs are dulness and bronchial breath sounds at the right upper lobe. Numerous crepitations and distant breath sounds are present at the right base.

An X-ray film (figure 24) shows old-standing lesions in the right infraclavicular region and midzone and some scattered points of calcification at the right base. The right diaphragm is elevated and the costophrenic sulcus is obscured.

A bronchogram (figure 25) reveals extensive bronchiectasis of the right lower half of the lung field.

This case shows how such an important feature as extensive bronchiectasis can be missed when a bronchogram is not done.

*Case 15:* O.P., European female, aged fifteen. In April, 1940 she complained of headaches and was told that her tonsils were "septic." She had frequent sore throats. She coughed a little and swallowed sputum. She is a healthy looking school girl. Her temperature and pulse are normal. Her sputum was found to be negative for tubercle bacilli on numerous occasions. Clinical examination revealed no abnormal physical signs.

An X-ray film (figure 26) shows infiltration at the right base.

A bronchogram (figure 27) shows collapse and bronchiectasis at the right base; midzone bronchi normal.

This is an interesting contrast to the preceding case. The condition is not tuberculous but there is little difference in the ultimate pathological changes of the bronchi.



FIG. 20. Upper left; FIG. 21. Upper right; FIG. 22. Lower left; FIG. 23. Lower right





FIG. 24. Upper left; FIG. 25. Upper right; FIG. 26. Lower left; FIG. 27. Lower centre; FIG. 28. Lower right.

*Case 16:* O.P., European male, aged fifty. He was always healthy. While working strenuously on a ship he coughed up some blood, but has been quite fit ever since. He was sent to hospital for investigation. He is a fit looking European male. His temperature and pulse are normal. He does not raise any sputum.

A customary X-ray film did not show anything definite, with the exception of a slight decrease in aeration throughout the left lung.

A bronchogram (figure 28) shows bronchiectasis at the left apex. The rest of the bronchial system appears normal.

This nontuberculous case is included as a contrast to the preceding one. Although the devastation produced in this case is not as great, the type of bronchiectasis is just the same in both cases.

#### DISCUSSION

When we found how every case of pulmonary tuberculosis told the same tale when we explored its bronchial system we felt like Keats with Chapman's Homer:

"Then felt I like some watcher in the skies  
When a new planet swims into his ken,  
Or like stout Cortez when with eagle eyes  
He stared at the Pacific—and all his men  
Look'd at each other with a wild surmise—  
Silent, upon a peak in Dorien."

We commenced this paper by stating our findings so that in this place there is no need to recapitulate these beliefs. The cases we have shown have been of all types of pulmonary tuberculosis from early exudative lesions to mixed exudate and productive lesions and finally to cases of chronic productive disease. In contrast we have shown nontuberculous septic conditions of the lung and in each instance the bronchograms have given a truer picture of the lung disease than history, physical signs or conventional radiographs.

Bronchography depicts living pathology; it depicts bronchial changes as a military map does a devastated countryside. It demonstrates the phases of the war from the first invasion to the ultimate defeat of the enemy and shows the twisted bronchi, the dilated tortuous conduits left after the battle, the gaping holes in a peaceful tissue and the attempt of the normal lung left to fill the gap and carry on the functions of respiration under great difficulties.

It shows much of our collapse therapy is futile and that perhaps the future treatment of pulmonary tuberculosis will be a direct intrabronchial attack.

#### SUMMARY

The geographical pathology of certain types of lung disease is demonstrated by means of bronchography. The value of the bronchogram is shown by contrasting conventional radiograms with bronchograms.

The conclusion is reached that the most important factor in both pulmonary tuberculosis and septic infections of the lung is bronchial or bronchiolar block

with the resulting atelectasis, cavitation or bronchiectasis, and that the pathological processes of pulmonary tuberculosis are adequately explained on this basis.

The conclusion is also reached that physical signs are not to be relied upon as accurate indications of a pulmonary process.

#### SUMARIO

Por medio de la broncografía queda revelada la patología geográfica de ciertas neumopatías. La comparación de las radiografías clásicas con los broncogramas revela el valor de los últimos.

En este trabajo llegase a la conclusión de que el factor más importante tanto en la tuberculosis pulmonar como en las infecciones sépticas del pulmón, es el bloqueo bronquial o bronquiolar con la resultante atelectasia, cavitación o bronquiectasia, y que sobre esa base explícanse adecuadamente los procesos patológicos de la tuberculosis pulmonar.

También se saca la conclusión de que no hay que atenerse a los signos físicos como indicaciones exactas de un proceso pulmonar.

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# ROENTGENOLOGY OF THE MASSIVE CONGLOMERATE LESIONS OF SILICOSIS<sup>1</sup>

MORTIMER RICHARD CAMIEL

The roentgenological recognition of the massive conglomerate lesions of silicosis is often difficult. The condition is frequently confused with pulmonary malignancy, infections or atelectasis (1-6, 9, 10). The therapeutic, surgical and medico-legal implications of such an error are important.

The appearance of such lesions is especially confusing when an occupational history is not elicited or improperly evaluated. The difficulty in diagnosis increases when the typical nodulation of silicosis is absent (3).

There is, however, a group of the conglomerate lesions of silicosis in which the roentgenological picture is so typical that the diagnosis may be made from the roentgenogram itself—even in the absence of characteristic nodulation and an occupational history. The basic appearance of the lung of this group is as follows:

- 1: Subapical or subclavicular location of the lesions is most common; the process is often located in the apices of the lower lobes.
- 2: The lesions are almost invariably bilateral.
- 3: There is a tendency toward symmetry.
- 4: There is frequently a clear zone of emphysema surrounding the lesions and separating them from both the hila and the chest wall. The separation from the hila is an important sign, since it excludes at once lesions which might arise in the hilar lymph nodes, such as Hodgkins disease.
- 5: Emphysema over the remainder of the lung fields is almost invariably present.
- 6: The position of the lesions is usually longitudinal. Gardner (3) points out that they may lie at right angles to the ribs. The shape of these lesions do not form standard patterns, as may be seen with neoplasms or infarction, but their longitudinal position is helpful in recognition.
- 7: Confirmatory typical nodulation may be present.
- 8: The lesions in the separate lung fields incline toward a similar density and appearance. With primary carcinoma or tuberculosis on one side with spread to the other the appearance in the opposite lung field is different. The density may be much greater than with neoplasms.
- 9: Fibrous strands are frequently seen radiating outward from the lesions.
- 10: Diaphragmatic deformities are frequent (4, 7, 8). Limitation of diaphragmatic motion is common.
- 11: The trachea is usually in the midline.

The following 2 cases exemplify the criteria enumerated above.

## CASE REPORTS

*Case 1:* F. L. The patient was a 51 year old, white, Italian male, who entered the Triboro Hospital for Tuberculosis on April 2, 1942. Following a chest roentgenogram elsewhere

<sup>1</sup> From Triboro Hospital, Jamaica, Long Island, New York. From the service of Dr. A. L. Bachman, who is serving with the Armed Forces.

he was referred to us with a diagnosis of pulmonary tuberculosis. His chief complaint was marked cough, with some expectoration and considerable dyspnea of two months' duration.

On physical examination the signs pointed to disease in both lung fields. Repeated sputum examinations and cultures were negative. The temperature was flat. The vital capacity was 3,000 cc. The red blood count was 5.08 million with 100 per cent hemoglobin. The white cell count was 9,400 with 50 per cent polymorphonuclear leucocytes,

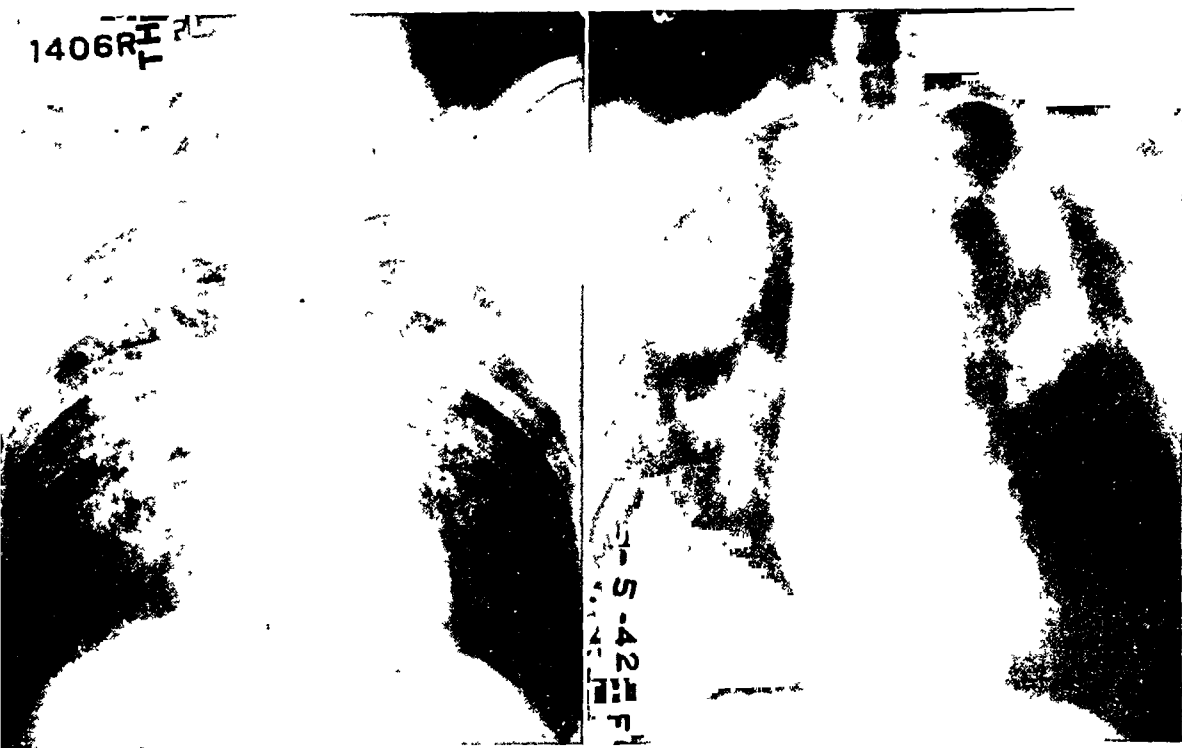


FIG. 1. (Left). Case 1. The typical appearance of a massive conglomerate silicotic process is shown. No complete occupational history was obtained at the time of the examination. Note the marked similarity of this appearance to figure 3, which is a roentgenogram of a man who was a miner for twenty-two years. This patient remembered later that he worked in a terra-cotta factory during his youth. He inhaled stone and cement dust for three years.

FIG. 2. (Right). Case 1. Tomogram. Massive conglomerative lesions of silicosis

46 per cent lymphocytes and 3 per cent monocytes. The Wassermann reaction was 4 plus. Urine examinations were negative. Sputum examinations for fungi were negative.

His pulmonary picture was attributed to one of the following possibilities: sarcoidosis, fungus infection, lymphoblastoma, such as Hodgkins disease or lues.

His course in the hospital remained unchanged. Four months after admission, he was discharged with the following diagnosis: Undiagnosed disease of the lung. No clinical evidence of tuberculosis. Syphilis.

A review of the roentgenograms (figures 1 and 2) revealed the typical appearance of silicosis, as described above. Upon further questioning the patient remembered that he had worked in a terra-cotta factory for three years during his youth and, at that time, he inhaled stone and cement dust.

*Case 2: A. J.* The patient was a 47 year old, white male of Portuguese origin, who entered Triboro Hospital for Tuberculosis on February 4, 1944. He was referred here by a regional tuberculosis health office with a diagnosis of tuberculosis. His chief complaint was that, for almost a year, he had felt a "lump" in his stomach which made breathing difficult. He suffered from night sweats, cough and weight loss of from five to ten pounds. His shortness of breath had become more marked and his cough was productive of white sputum. His relevant past history was that he had been a miner for twenty-two years, between 1921 and 1943. Because of dyspnea he was told to give up working in the mines, which he had done three months before admission. There was no tuberculosis contact.



FIG. 3. (Left). Case 2. Massive conglomerate lesions of silicosis. The patient had been a miner for twenty-two years

FIG. 4. (Right). Case 2. Tomogram. Massive conglomerative lesions of silicosis

On physical examination the thorax expanded symmetrically. There was impaired resonance over the entire left upper lobe and left back posteriorly with diminished breath sounds with an occasional fine subcrepitant râle. There was some clubbing of the fingers. The impression was that he had chronic pulmonary tuberculosis.

His temperature was flat. His urine and sedimentation time were normal. His red count was 5.19 million with 96 per cent hemoglobin. His white count was 9,000 with 58 per cent polynuclear, 41 per cent lymphocytes and 1 per cent monocytes. The vital capacity was 3,200 cc. Sputum examinations were negative on smear and concentrate. The Wassermann reaction was negative. The chest roentgenograms (figures 3 and 4) revealed the typical appearance of silicosis with conglomeration, as described above.

#### DISCUSSION

These cases exemplify that group of silicosis with massive conglomeration which can be recognized roentgenologically. While the clinical aspects are of

great importance when properly evaluated, the occupational history is often not elicited and the ability to make the diagnosis from the X-ray films alone is significant.

Pendergrass (8) makes an interesting observation regarding the zone of emphysema surrounding the lesions. If this is obliterated by an extension of the lesions outward to the periphery of the thorax or to an interlobar fissure, he believes that this might indicate an associated active infection. We believe that obliteration of the mediastinal emphysematous zone might indicate the same thing. Gardner (3) points out that, when the borders of the conglomeration are soft and hazy, an active underlying process is suggested. Tomography may be of aid in defining the gross underlying process (figures 2 and 4).

The general basic characteristics here enumerated may be recognized at a glance, in the cases presented. In some cases, however, the pathological appearance has become so complex that recognition becomes much more difficult. Nevertheless, close scrutiny of the films may reveal enough of these basic characteristics to afford a great help in diagnosis.

These 2 cases emphasize the need for a detailed occupational history. It is known that the first patient inhaled stone dust for three years. The second patient was a miner for many years. A vague history of stone-dust inhalation or mining is insufficient. For logical proof, positive evidence of free silica in the inhaled dust must be obtained before an occupational hazard is established. In these 2 cases, however, the roentgenological findings are so typical for silicosis that one might assume that free silica was inhaled. In the absence of pathological proof, however, the diagnosis of massive conglomerate lesions of silicosis remains a presumptive one.

#### SUMMARY

1. The roentgenological criteria for the diagnosis of a group of conglomerate lesions of silicosis are enumerated.

2. Using these criteria, the correct diagnosis may be suggested from the roentgenographic study alone, even in the absence of a confirmatory occupational exposure.

3. Two cases with suggestive occupational exposure are presented. In addition to the occupational history, exact knowledge of the type of dust inhaled is necessary for the logical establishment of a hazard. The typical roentgenological findings of silicosis in these cases are in accord with the inhalation of free silica.

#### SUMARIO

1. Enuméranse las pautas roentgenológicas para el diagnóstico de un grupo de lesiones conglomeradas de silicosis.

2. Tomando esas pautas, el estudio radiográfico por sí solo puede sugerir el diagnóstico correcto, aun sin haber exposición profesional que lo confirme.

3. Preséntanse dos casos con antecedentes indicativos de exposición profesional. Además de tales antecedentes, se necesita un conocimiento exacto de la clase de polvo inhalado para establecer lógicamente el riesgo. En estos casos

los típicos hallazgos roentgenológicos de silicosis armonizan con la inhalación de sílice libre.

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## EFFECT OF ALTITUDE ON ABNORMAL ACCUMULATIONS OF AIR IN THE CHEST<sup>1</sup>

EZRA BRIDGE AND EZRA BRIDGE

Because aircraft provide swift, comfortable transportation, physicians can be expected to advise air travel for their patients. Even so, flight will be hazardous for those with certain diseases. We propose to examine the nature of this hazard for patients harboring abnormal accumulations of air in the chest.

Lovelace (1) has briefly discussed the danger of exposure of patients with pneumothorax to reduced atmospheric pressure with special reference to transport of patients by airplane.

### CHANGES IN GAS VOLUME WITH PRESSURE

Boyle's law states that, under conditions of constant temperature, a given volume of gas varies inversely with the pressure exerted upon it; the law for ideal gases is expressed by the following equation:

$$V' P' = V P$$

wherein:

$V'$  = volume of gas at variant pressure

$P'$  = variant pressure

$V$  = original volume of gas

$P$  = original pressure

In the present problem a correction for vapor pressure at body temperature must be made because abnormal accumulations of air in the chest will probably be saturated with water. At sea level (760 mm. Hg) water vapor exerts a pressure of 47 mm. Hg at 37° C. The equation for computing the change in volume of water-saturated gas at sea level when exposed to the reduced pressure at any altitude is as follows:

$$V' = V \times \frac{P}{P'} + (V' - V) \times \frac{47}{P'}$$

The percentage increase in volume attained at any altitude is derived as follows:

$$\% \text{ increase in volume} = \frac{V' - V}{V} \times 100$$

The percentage increase in volume at altitudes up to 30,000 feet is given in figure 1.

Obviously, a volume of gas enclosed by walls rigid enough to prevent expansion will undergo no change when the enclosing vessel is exposed to reduced pressure. Nevertheless, the difference in pressure between the inside and outside of the vessel tends to expand its walls. This pressure differential is simply the difference between the pressure at sea level and that at altitude. Furthermore, this

<sup>1</sup> From Iola Sanatorium, Rochester, New York.

pressure differential would stretch the walls of a semi-rigid vessel until the tension of the walls equaled the pressure differential.

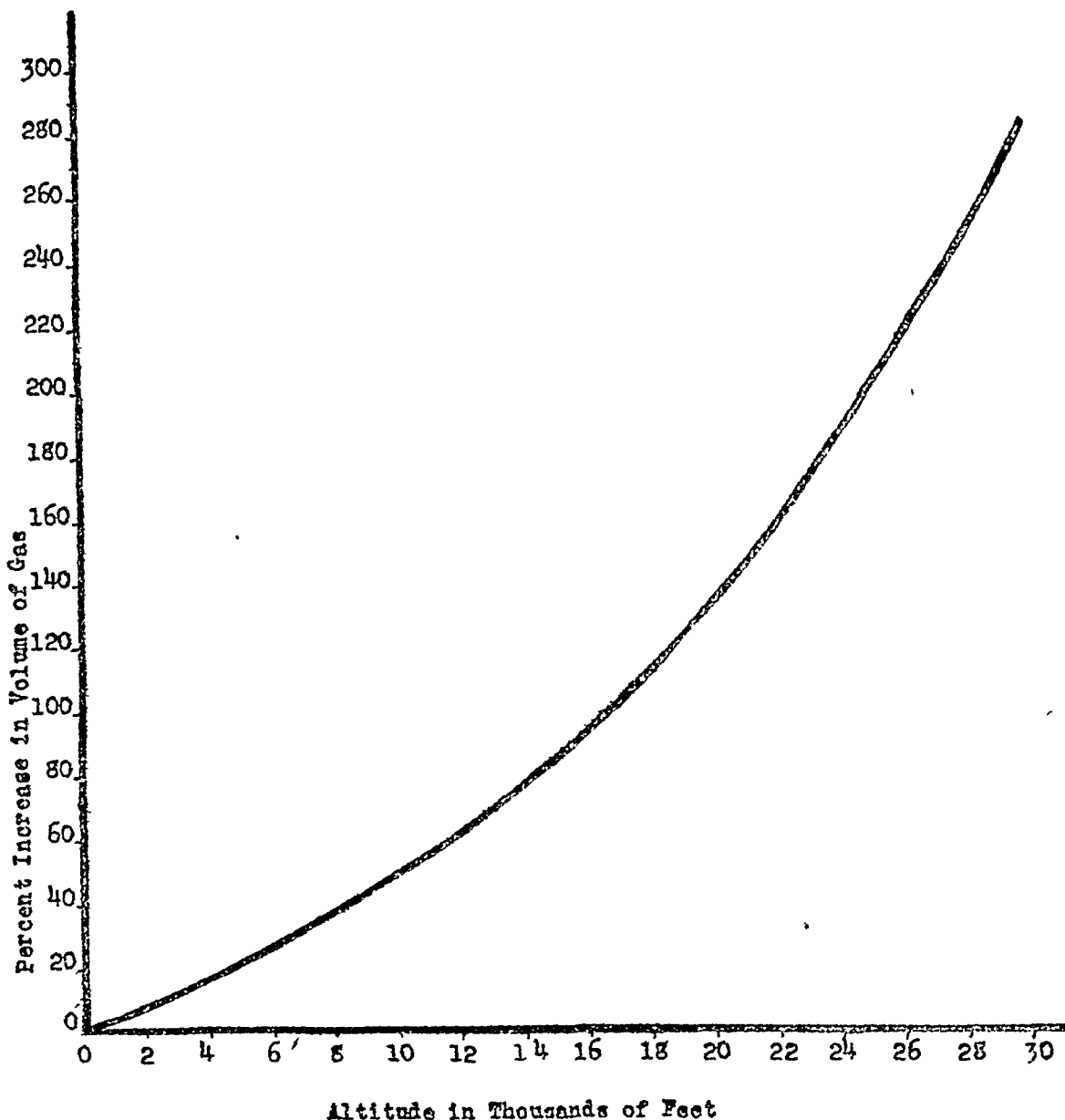


FIG. 1. Change in volume of freely expanding gas from sea level to 30,000 feet above sea level.

The descent from altitude encountered in moving from a mountain community to one in the lowlands is associated with changes in barometric pressure sufficient to compress gases. Correcting for the resolution of water from the vapor phase, the equation for computing the decrease in volume of gas when subjected to increased pressure at 37° C. is as follows:

$$V' = V \times \frac{P}{P'} - (V' - V) \times \frac{47}{P'}$$

Table 1 gives the per cent of original volume of gas at various altitudes expected during descent from communities up to 10,000 feet above sea level.

TABLE 1

*Per cent of original volume of gas compressed by increasing barometric pressure from various altitudes to sea level*

ALTITUDE IN THOUSANDS OF FEET	PER CENT OF ORIGINAL VOLUME OF GAS				
0	66.9	72.7	79.0	85.5	92.5
2	72.4	78.5	85.3	92.4	100.0
4	78.4	85.0	92.3	100.0	
6	84.8	92.1	100.0		
8	92.1	100.0			
10	100.0				

#### POTENTIALLY HAZARDOUS CHEST LESIONS

Those lesions of the chest involving abnormal accumulations of air and presenting hazards for the patient who would travel in aircraft are:

##### 1. Pneumothorax:

- A. Uncomplicated types: unilateral, bilateral, intrapleural or extrapleural.
- B. Complicated types: visceroparietal adhesions, mediastinal hernia.

##### 2. Pulmonary cavity:

- A. Closed communication with a bronchus occasioned by fluid within the cavity, or
- B. Intermittent communication with a bronchus occasioned by "check-valve" structures.

##### 3. Emphysema:

- A. Pulmonary.
- B. Mediastinal.
- C. Subcutaneous.

Civil aircraft usually fly at altitudes less than 10,000 feet above sea level, but higher altitudes may be occasioned by mountainous country or storms. Exposure to lowered barometric pressures will cause expansion of abnormal accumulations of gas in the patient's chest depending on the rigidity of the tissue walls enclosing the gas. One may regard the enclosing walls of uncomplicated intrapleural pneumothorax as presenting the least resistance to gaseous expansion because the elasticity of the lungs encourages their collapse. The hazard of reduced barometric pressure is magnified by increasing altitude, and the greater the amount of gas producing the pneumothorax the greater will be the collapse of lung. A patient carrying 1,000 cc. of intrapleural air at sea level will have the equivalent of 1,270 cc. at 6,000 feet, 1,490 cc. at 10,000 feet and 2,120 cc. at 18,000 feet. With an increase in effective pneumothorax, there can be a contralateral shift of the mediastinum and partial collapse of the opposite

lung. It is apparent, then, that moderate altitudes will offer undue danger and that pneumothorax which is tolerable for the patient at sea level could endanger his life at altitude. Pneumothorax complicated by mediastinal hernia or by visceroparietal adhesions offers the risk of increasing the hernia or rupturing the adhesions. The greater the tension of the adhesions, the more likely they are to rupture.

Rigid walls occasioned by thickened pleura or by extrapleural pneumothorax will be subjected to pressure differentials also proportional to altitude. These pressures could cause dissection of the pleura and even severe pain of pleural origin.

A pulmonary cavity, unless communicating freely with a bronchus or possessing very rigid walls, could be expected to expand because of the pressure differential and the tendency of surrounding lung tissue to collapse. Expansion of the cavity might rupture its walls, disseminate infective material or induce hemorrhage by severing vessels traversing the cavity.

During decompression, particularly rapid decompression, some persons are troubled by expansion of intestinal gas. Though protrusion of the abdominal wall would reduce upward pressure on the diaphragm, it is conceivable that this pressure could add its fraction to the respiratory embarrassment impelled by exposure of pneumothorax to reduced barometric pressure.

Expansion of gas producing mediastinal and subcutaneous emphysema could cause further dissection by emphysematous tissue when subjected to reduced pressure. The coalescent alveoli of pulmonary emphysema are supposed to produce expiratory difficulty by being pressed about the alveolar openings of terminal bronchioles in such a fashion as to constrict if not occlude them. Air is thereby trapped in the alveoli or its expulsion is impeded. Adjustment to retained air might be made at altitude, but during ascent the patient with pronounced emphysema of the lungs could suffer increased dyspnea due to expansion of air trapped in the alveoli.

Patients with pneumothorax or with a pulmonary cavity having an obstructed bronchial communication could be expected to show a decrease in pneumothorax or in the size of the cavity when removed from a community at high altitude to one at low altitude. Thus a patient with 1,000 cc. of intrapleural air at 6,000 feet would have a reduction in pneumothorax to 669 cc. when brought to sea level. If the original degree of pulmonary collapse were to be maintained, 331 cc. of air would have to be added.

#### CRITERIA FOR SELECTING PATIENTS TO TRAVEL BY AIR

Because the tolerance to reduced vital capacity varies from patient to patient, criteria for selecting patients to travel by air are difficult to determine. We believe the following contraindicate air travel for patients with abnormal accumulations of air in the chest:

1. Cyanosis or dyspnea.
2. Recent hemothysis.
3. Visceroparietal adhesion.

4. Mediastinal hernia.
5. Mediastinal displacement.
6. Pulmonary cavity containing fluid or with signs of intermittent bronchial communication or with closed bronchial communication.
7. Mediastinal emphysema.
8. Pulmonary emphysema with dyspnea.

We believe air travel should be restricted to those patients who would have no respiratory or circulatory distress and no physical discomfort if the abnormally accumulated air in the chest were doubled. If the physician can be sure that his patient would not have to fly above 10,000 feet, the critical increase in air might be reduced to 50 per cent. He should insist that his patient breathe pure oxygen through a suitable mask if there is the slightest possibility of hypoxia due to diminished oxygen tension at altitude and impaired vital capacity engendered by collapsing lung. He should remove an adequate amount of intrapleural or extrapleural air prior to flight if there is a possibility of dangerous increase in effective pulmonary collapse at altitude.

#### SUMMARY

The hazards of air travel for patients with abnormal accumulations of air in the chest are discussed.

#### SUMARIO

Discútense los riesgos que entraña la navegación aérea para enfermos que tienen acumulaciones anormales de aire en el tórax.

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# TUBERCULIN TESTING OF PREGNANT WOMEN<sup>1</sup>

MARTIN J. SEID

Previous reports in the literature have indicated that routine tuberculin testing of prenatal clinic patients is a procedure of great value in the detection of co-existent tuberculosis. Pulmonary tuberculosis is apt to be particularly severe in the young child-bearing age group.

There are few reports of routine tuberculin testing of prenatal clinic patients in the literature. This leads to the belief that this procedure has not enjoyed the wide-spread adoption that it merits. Ianne and Muir (1), reporting in 1939 on a survey similar to ours, found "a search of the literature was made with the help of Dr. Kendall Emerson of the National Tuberculosis Association. This revealed that tuberculin testing has not been followed routinely in obstetrical clinics. According to the Bureau of Maternal Welfare in Washington nothing bearing on this work is on file in the U. S. Library."

We have been able to find only one other report, where the tuberculin test was used in pregnant women to screen out possible cases with active lesions, that by Maeder and Myers (2) who, in 1940, tuberculin tested 2,350 pregnant women entering the Minneapolis General Hospital. The chests of all reactors were then examined with X-ray films. X-ray findings of 841 reactors were: possible primary complex 135; probable reinfection type lesions 26; of these, 17 were minimal, 4 moderately advanced and 5 were far advanced.

Ianne (1) used the tuberculin test as the first screen. Reactors were fluoroscoped. X-ray films were then taken of all suspicious looking chests; 691 pregnancy clinic patients were thus routinely examined; 248 reactors were found. X-ray examination brought to light 12 cases of reinfection type disease, of which 10 were minimal, one moderately advanced and one far advanced.

Other workers have used fluoroscopy as the first screen; X-ray films being made in all suspicious cases. Unfortunately this requires much time, equipment and experienced operators. Perlberg (3) examined 238 pregnant women and felt that few tuberculous lesions which showed up on X-ray films would have been missed by an experienced man on fluoroscopy. Eisele and Mason (4), using this method on prenatal clinic patients, found 1.06 per cent of those examined to have tuberculosis. They objected to the routine use of the tuberculin test on the grounds that almost all adults would be positive anyway.

It is our opinion that this view is not valid when applied to obstetrical clinic patients. We found 38 per cent of the women entering Stanford prenatal clinic sensitive to tuberculin. Ianne (1) reported 41 per cent of the women tested in his survey were reactors. Maeder and Myers (3) found that only 31.5 per cent of the women they tested gave positive reactions.

Furthermore in the 20 to 25 year age group of prenatal clinic patients tested by us only 25 per cent were found to be reactors.

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## PROCEDURE

One thousand women entering the Stanford University Medical School prenatal clinic were tuberculin tested between January, 1940 and May 1942; 0.1 mg. of OT was used in 948 cases, and PPD in 52 cases; 12 women failed to return for reading. Ages were between 16 and 43 years. Twenty-five per cent of the reactors were in the 20 to 25 year age group. Three hundred and eighty women, or 38 per cent of the women, reacted to tuberculin.

Our procedure was to fluoroscope those who had positive tuberculin tests and X-ray those indicated by the fluoroscopic findings; thus, 380 women were fluoroscoped; 33 of these were X-rayed. Following this course we found 14 women with reinfection type of pulmonary tuberculosis; 4 of these had moderately advanced and 10 minimal lesions. No far advanced lesions were found; 82 cases with healed (?) primary lesions were found. The remainder, that is, 284 women had normal roentgenological findings.

## SUMMARY

1. The importance of routine tuberculin testing of pregnant women is emphasized.
2. Reactors should be fluoroscoped and X-rayed as indicated.
3. The results of tuberculin testing of 1,000 pregnant women are reported.

## SUMARIO

1. Recálcase en este trabajo la importancia de la comprobación sistemática de las gestantes con tuberculina.
2. En los casos positivos deben ejecutarse roentgenoscopias y radiografías según esté indicado.
3. Preséntase el resultado de la comprobación con tuberculina de 1,000 gestantes.

Much appreciation is expressed to Dr. J. J. Niebauer for his excellent bibliography, and arrangement of this paper. My appreciation also goes to Dr. Philip H. Pierson and Dr. Ludwig A. Emge.

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## PATIENT EDUCATION IN REHABILITATION<sup>1</sup>

HELEN M. BECHT<sup>2</sup>

I should like first, if I may, to explain the subject which was assigned to me—*Patient Education in Rehabilitation*. Perhaps it seems clear—but let's analyze it, to see.

The word "patient," in its usual usage, as applied to persons securing rehabilitation help, signifies a person who is still in the hospital or sanatorium. Despite the risk of straying from my subject, if, perchance the subject was to impose those limits, I shall discuss not alone "patient" education, but "client" education as well, and include for consideration those persons who have left the hospital and are again in the community under out-patient care.

Education, itself, may, for entire clarity, need definition. We conceive it in its pure sense of development and growth, from the Latin origin *educo*—to lead out—and not in the sense of superimposed learning which provides a coating, but does not penetrate beyond the outer surface. Education, as we shall discuss it, has no resemblance to a "duco" paint job!

And what of rehabilitation? In this paper we shall think of it as a process of education through which a person goes to arrive at optimum adjustment—adjustment to his own health, to his family, his friends, to his work, his play, and to the society in which he finds himself. We must admit that this process may be pursued to a degree with self-direction, but contend that, since tuberculosis most frequently exists where other socio-economic problems also are found (bad housing, malnutrition, poor working conditions, to mention but a few), the process is likely to be one in which outside leadership is not only highly desirable but often indispensable. And we shall contend that the process should start at the time of diagnosis.

To say that there never was a person who had tuberculosis who did not need education may seem, to some, an extreme statement, and yet that is what I, who am not fond of extremes, am forced to believe. From my experience, to date, I can say that I have never known an individual to arrive at the Queensboro Tuberculosis and Health Association for rehabilitation help without needing it, and that of many tuberculous persons, from all groups, whom I have known, outside of my office, already fully rehabilitated and back in the swing of active life, there has been none who has not confessed that somewhere along the line he needed it—education of a very special kind—education which took into account his physical condition and which explained it to him in terms which he could apply to day-by-day living.

Of the 750 persons with whom we have worked actively in our department, only 2, at the time they came to us, were, in any reasonable fashion, prepared to accept

<sup>1</sup> Presented in the symposium on *Channels for Wider Community Participation in Tuberculosis Control* at a session of the Public Health Section at the 40th annual meeting of the National Tuberculosis Association, Chicago, Illinois, May 10, 1944.

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the limits which their disease had imposed upon them with sound intelligence and with emotional balance.

On the one hand, clients arrive with full medical approval for activity, fearful to embark upon it. On the other, they come without their physicians' sanction for any activity at all and champ at the bit to "get going" and to make up for the time they "lost" in the sanatorium.

If a client, whose physician has given tentative approval to two hours' daily activity, discloses to us the fact that he is already working eight hours a day, plus over-time, plus an hour and a half commutation to and from work each day—somewhere, we submit, proper education has been lacking. If another client, apparently cured from a minimal infection and approved, at the time of his first contact with us, for eight hours' work a day (and approved for eight long years before he ever reached us) is still fearful of attacking even one hour's employment, education again has been sadly absent. If, when we tell a despondent and spiritless young man, newly discharged from the hospital after a nine months' "cure," that there are ways back, and the hardest part of the road has probably been covered, that young man shudders and says, "My God, why didn't some one tell me this before," education, if it existed in any form, was, we think, a failure.

That the essence of 75 per cent of our out-patient rehabilitation is still health education seems to me to indicate less that this is a correct proportion of emphasis than that insufficient emphasis has been put upon it during the earlier period of physical cure.

What education is needed in the hospitals? What do the patients want and why do they want it? Ask them, and from their replies know that they are not so much interested in the size (in millimeters) of the cavities in the left sides of their chests as they are in what those cavities mean to them and what their presence will do to their lives. Who cares whether the cavity is in the third or the fourth intercostal space? Surely not the patient—particularly if he has had six grades of grammar school. If he be a medical student, or if he be over-interested in himself—(and the former is less likely than the latter)—there is reason for an interest in disease; but even if he be a medical student we should prefer that during the period of his cure his interest be aroused in health rather than in disease. If he be overconcerned with himself there is every reason in the world to divert his interest and to stir it in the direction of how men live, rather than in how men die. Tuberculosis patients, by and large, are not equipped to understand the technical intricacies of epidemiology, of pathology and of progressive and retrogressive disease, nor is there any reason why they should be. They are equipped and interested to learn what health or the loss of part of it means to them and how it is related to driving a bus, to running a milling machine, to going to their weekly club meetings, to living with their families, to taking courses in Business English and to paying their rent on time.

These are the things for which no busy doctor can be held personally responsible, but these are also the things that every intelligent community should, in some way, provide for its tuberculous citizens. These things, in our opinion, are

basic, but education in health, though it should be at the core of hospital instruction, is not, we think, enough.

Sound bodies can house stagnant or troubled minds. Troubled minds can create broken spirits. And if we wish to seem less philosophical, we can say, in more practical words, that troubled minds and broken spirits do not contribute to tuberculosis control, do not contribute to patient coöperation in cure, do not act as safeguards against recurrence and do not protect a society from the too early return of patients half cured and almost wholly shattered. And we can say that education has proved that men's minds and spirits do not remain static from day to day and month to month and year to year. They change, by growth or by degeneration, as their bodies change, by growth or by decay. No mind, left fallow for too long a period, retains its resiliency. No spirit, left fallow for too long a time, maintains its "fight." Tuberculosis is not cured in a day, and not all patients, prior to their illness, have had experiences which have fortified them against the demoralizing inroads of empty time.

What education other than health education should be provided in the hospital no one can say, specifically, unless he knows the patient population concerned. Classes cannot intelligently be set up, correspondence courses planned, study groups formed nor individual plans made unless the interests, abilities and ambitions of the patient group be ascertained. And even that is not enough, for the kind of education which we advocate takes as a prime responsibility the creation of interests where none is apparent. Stimuli to interest are the essential tools of the educator, if he be a real educator who differentiates between teaching people and teaching subject matter.

Not every hospital can have on its staff educators who are prepared to attack every level of learning which the patient group may need—but every hospital should have, somewhere in its personnel, a person or persons who will have sufficient interest in patients as people, sufficient awareness of the vast range of individual differences among them, and sufficient consciousness of the facilities which its community provides to make some connection with the extramedical needs of patients and the opportunities which are available to meet those needs.

This is somewhat more difficult in simpler or more remote localities, where outside facilities are meager or far removed from the seat of the hospital; somewhat more difficult, but by no means the less necessary, and by no means an insurmountable difficulty. Wherever the institution and whoever the person responsible for extramedical services to patients, an educational program can be inaugurated provided hospital administration itself is convinced of its necessity. Wherever it be, and by whomever done, it will fail its purpose utterly unless it be founded on full coöperation with the medical policies of the institution and unless it take no step for educational activity which does not have full medical approval.

Physicians must decide amount of activity and kind, in terms of physical strains and conditions, relating it to the physical tolerance of patients. Educators and rehabilitation workers (and patient education is, we think, an integral part of rehabilitation) decide activity in terms of recreational, academic, cultural

and vocational benefit, relating it to the intellectual, emotional, social and vocational capacities of the patients whom they serve and grading it in kind and amount according to medical prescription. Each alone does less than half a job. Both, working together, can accomplish a maximum of benefit not only to the individual patient, but to the community to which he will return and, more important even than that, to the more complete control of tuberculosis and its concomitants.

Many hospitals who claim no rehabilitation program have pieces of rehabilitation already in action—sometimes a library, sometimes a social service department, sometimes an occupational therapy department, sometimes all three or even more. All these are parts and highly essential parts. Each, however, uncorrelated with the others and incompletely correlated with the medical service, fails its opportunity for full helpfulness and may fail its chance for any. A library, with every shelf filled to capacity with current best sellers, and with wide circulation records, can still be incomplete unless it knows the reading needs of the persons whom it is designed to serve, and unless it works in the direction of meeting those needs. Not everyone is nourished by a monodiet of best sellers. Detective stories and “Westerns” may not make a man a top-flight mechanic on small parts when he is ready for normal work, but they may help to make him a more satisfied person and a more balanced one, if they do not continue to make up his entire “five foot shelf.” Health education texts, prepared in style and format which have been tested with sample patient groups to assure their appeal, we think no library should omit. Texts on any number of academic subjects, though dry to some and unnecessary to others, can be main-springs to the education of those who need them. Vocational pamphlets for general orientation and specific job information are as necessary. Since all of life is not spent at work, we should like to see some poetry, some art, some music, in the library. When we speak of the art field we wish again to emphasize that Boogie Woogie may be as important to one person as Bach to another.

Occupational therapy, as well as the library, should have as its central quality a flexibility which will assure the kind of activity which will be of greatest significance to the persons engaging in it. Though all of life is not one's work, as we have already said, we do have to face the fact that the majority of one's waking hours are spent at work as apposed to any other single activity. For this reason we think that Occupational Therapy falls down if it be concerned only with leisure time employments, with recreational, craft or even cultural pursuits.

In the hospital, which has a good plan of education, can be started activity which has meaning. There can be born or nurtured the desire and the fact of being busy at something which is not confined to the lives of men and women who are ill. There should be, we think, academic training and prevocational exploratory opportunities. There may be actual vocational activity, either on a training level or actually on a work level. The Arma Company, in Brooklyn, and the Navy hospitals with which it has worked have demonstrated that even men in bed can be employed usefully and gainfully, that they can utilize the

hospital as a place not only for physical restoration, but as a place which conserves the skills and interests of patients and weans them from the insecurities which illness breeds.

Social service workers are educators as well, educators who have sometimes to do things for patients, but whose aim always should be in the direction of helping people to do things for themselves.

Librarians, occupational therapists, social workers, nurses, teachers, all have a part in the total program, all are educators of a kind, all are doing rehabilitation of a sort, but the work of all must be properly channeled and properly integrated each with every other, and all with medical supervision to have full value. And I do not mean to imply that the coördinator (and I think of the rehabilitation worker in that sense) must be some special new breed of human being who has all the knowledge and all the skills which go into the total program. As I see it, no one person could have, for rehabilitation and patient education touch too many fields to make it possible for one poor human to be competent in all of them. Whoever the coördinator, he must be a person who is aware of the functions of all of the fields which we have mentioned as parts of the total service and who has a healthy respect for each. He must know enough of health not to prescribe, himself, for disease. He must have a research attitude toward his job. He must be free from prejudices and from a fear of tuberculosis. He must respect the individuality of the patients for whose service he is employed, and be trained in one of the fields which has taught what service to the individual means. He must know enough of occupations to be able, after careful interviews with patients, to evaluate the abilities and potentialities of each so that his counseling is as sound vocationally as it is from a health point of view; and so that classes, lectures and other educational group activities reach those to whom they will be of greatest benefit.

He must know his own institution or organization—to know where lie its strengths and its weaknesses; so that he may utilize its resources wisely. He must know his community; so that he can draw upon it for the necessary services which his own organization may not yet be able to supply. In the absence of specialized services in his own organization he must draw upon aptitude testing services, boards of education and training centers of all sorts, outside social agencies, service clubs, libraries, publishing houses, museums, churches, employers, employment services—all for the specific information or service which he is called upon to provide. And, in the absence of specialized services even in his community, it is important that he be a person of sufficient skill to know when to refrain from services which he himself is not equipped to supply, and a person of sufficient administrative vision to work toward securing those services through additional paid or volunteer staff in his own organization.

He must know that a program which is not dynamic will be recognized as such by the patient group and that it will be likely to stimulate only a desultory interest on the part of most. He must recognize that, to have interest and vitality, program has to be linked to the patient's interests in the world outside the hospital, and that one of the strongest links to the outside world is likely to be

some activity which the patient hopes one day to resume. And he must through the whole process of education be seeing ahead to the time of probable discharge, when education and activity in the hospital can be used as the basis for sound action in the period immediately subsequent to discharge, and for the rest of the patient's life.

When this day comes, 75 per cent of the counseling time for clients already out of sanatoria will no longer be spent in health education. When this day comes, persons will less often reach the rehabilitation desk, outside, after having signed out, A.O.R. Then will individuals be ready, more easily, to fit into the less protected life at home, realizing their own responsibilities for the prevention of relapse. Then out-of-the-hospital rehabilitation workers can immediately call community agencies into action for real vocational help, for part-time activities which will accomplish physical hardening and training or work experience simultaneously. Then can rehabilitation follow-up concern itself with the total growth of the individual in his work and in his community life. Then can the rehabilitation worker, outside, have time to collect data which will refute public fears and prejudices which still act as barriers to many who have been ill. Then, and only then, we think, will rehabilitation and patient education really approach their coming of age.

#### SUMMARY

As an integral part of rehabilitation, patient education of the tuberculous, to be most effective, should start at the time of diagnosis. Rehabilitation, as a whole, is a process of growth for the individual in which he learns values and interrelationships of health, education, recreation, social and community responsibilities, in terms and concepts which have meaning for him, and on a level which he can apply to day-by-day living. Education in sanatoria will not only be a strong force toward stimulating patient coöperation during cure, but will minimize his confusion at time of discharge. Although health education should be at the core of such teaching, other education, based on the studied capacities, interests and ambitions of patients, should be provided, after medical prescription, at all levels of physical tolerance, from the time of bed-rest to the time full hospital activity is approved. Individual and class instruction should be planned to cover not only recreational and cultural interests, but academic, prevocational and vocational subjects which relate to life needs. Programs in which rehabilitation workers, occupational therapists, teachers, social workers, librarians and nurses exert their efforts under medical authority and under fully coöordinated direction, will use all outside community agencies to the end that such agencies can proceed with dynamic service when the day of discharge dawns.

#### SUMARIO

Como parte integrante de la rehabilitación, la educación del tuberculoso debe comenzar en el momento del diagnóstico para que surta su efecto máximo. La rehabilitación en conjunto representa un proceso de desarrollo en que el individuo

aprende nuevos valores y las interrelaciones de la salud, la educación, el recreo, las obligaciones sociales y colectivas, en términos y conceptos que tienen un significado preciso para él y en tal forma que los pueda aplicar a su vida diaria. En esa forma la educación en el sanatorio, no tan sólo constituirá una fuerza que estimulará la cooperación del enfermo durante el tratamiento, sino que atenuará sus problemas al darlo de alta. Aunque la educación sanitaria debe constituir el núcleo de dicha enseñanza, hay que ofrecer, cuando lo permita el médico, otra educación basada en la determinación de la capacidad, los intereses y los deseos de los enfermos, graduándola por la tolerancia física desde el momento del reposo en cama hasta que se autorice una plena actividad en el hospital. Los planes formulados deben comprender enseñanza individual y en clases que abarquen no tan sólo recreo e intereses culturales, sino también temas académicos, prevocacionales y vocacionales relacionados con las necesidades de la vida. Los programas de trabajo, en que los encargados de la rehabilitación, las ergoterapeutas, los maestros, las asistentes sociales, los bibliotecarios y las enfermeras realizan sus esfuerzos en debida coordinación bajo la dirección del médico, utilizarán todos los organismos cívicos del exterior a fin de que éstos puedan ofrecer sus servicios en forma dinámica cuando se acerque el alta.

# PENICILLIN IN THE TREATMENT OF PYOGENIC EMPYEMA COMPLICATING THERAPEUTIC PNEUMOTHORAX<sup>1</sup>

## Report of Two Cases

KIRBY S. HOWLETT, JR. AND DANIEL E. LESTER<sup>2</sup>

The successful use of penicillin in the treatment, without surgical drainage, of certain cases of pyogenic empyema caused by susceptible organisms is well known (1, 2, 3). Penicillin treatment of pyogenic empyema complicating therapeutic pneumothorax appears, by analogy, a rather obvious corollary. Such empyemata are, of course, commonly tuberculous and pyogenic. Butler, Perry and Valentine (3) report successful elimination of the pyogenic infection in one such case in their series of acute empyema cases. Penicillin has also been successfully employed for this complication by Riggins (4), and by Brian (5).

The serious prognostic significance of pyogenic empyema as a complication of pneumothorax in tuberculous patients, the ineffectiveness of the various pleural "antiseptics" previously tried and the tedious and time consuming character of even successful pre-penicillin therapy by surgical drainage, thoracoplasty and Schede operations, appear to warrant further reports of the special value of penicillin when this particular complication is encountered.

### CASE REPORTS

*Case 1:* A. W., a white woman aged 33, was admitted to Laurel Heights in January, 1940, with exudative tuberculosis with cavity involving the left upper lobe and with a very small lesion in the right lung. She was discharged as arrested on March 30, 1941, with an effective left pneumothorax of approximately one year's duration. Eight months later an acute pleural effusion occurred in the pneumothorax space, accompanied by marked toxemia and fever to 103°F. The pleural exudate, described as thin pus, was negative on smear and culture for both tubercle bacilli and pyogenic organisms.

Readmitted on December 27, 1943, the patient was treated by repeated aspiration without air replacement with a view toward complete obliteration of the pleural space. By mid-January, 1944, she was asymptomatic and afebrile, and pleural fluid, now clear, was greatly reduced in amount and rate of formation. The size of the free pleural space was also reduced to a small fluid pocket over the left apex. Several attempts to aspirate this on January 25 and 28, 1944 were unsuccessful. One week later the patient suddenly developed fever to 103°F., and X-ray examination showed an increase of pleural fluid (figure 1A). Aspiration produced 60 cc. of creamy pus, positive on smear and culture for *Staphylococcus aureus*.

Since we were familiar with the successful results observed in the experimental treatment with penicillin of certain pyogenic empyemata at the New Haven Hospital under the direction of Dr. Francis G. Blake, Doctor Blake was consulted and agreed to accept the patient for a trial of penicillin. The patient was transferred to the New Haven

<sup>1</sup> From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut, and the Department of Medicine, New Haven Hospital.

<sup>2</sup> Now located at the Albany Hospital, Albany, New York.



FIG 1A (Upper left) Case 1, February 10, 1944

FIG 1B (Upper right) Case 1, August 15, 1944

FIG 2A (Lower left) Case 2, June 8, 1944

FIG 2B (Lower right) Case 2, August 29, 1944

Hospital where treatment was started on February 17, 1944. On the first day of treatment she received 10,000 units of penicillin<sup>3</sup> intramuscularly and 30,000 units intrapleu-

<sup>3</sup> The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council



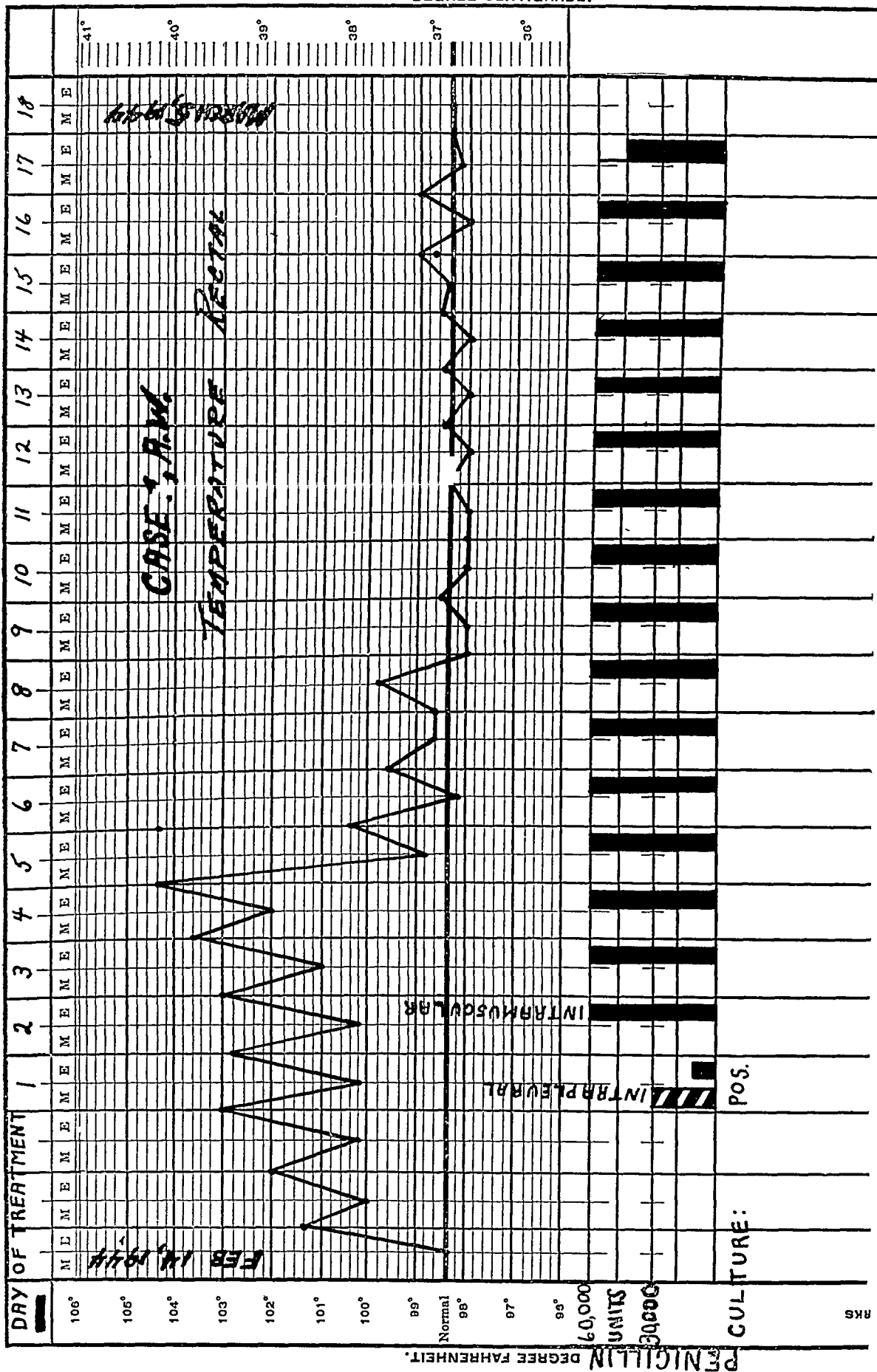


CHART 1

CHARTS 1 and 2. In both charts the solid columns represent the total daily amount of penicillin intramuscularly, the hatched columns the amount intrapleurally.

PENICILLIN DEGREE FAHRENHEIT.

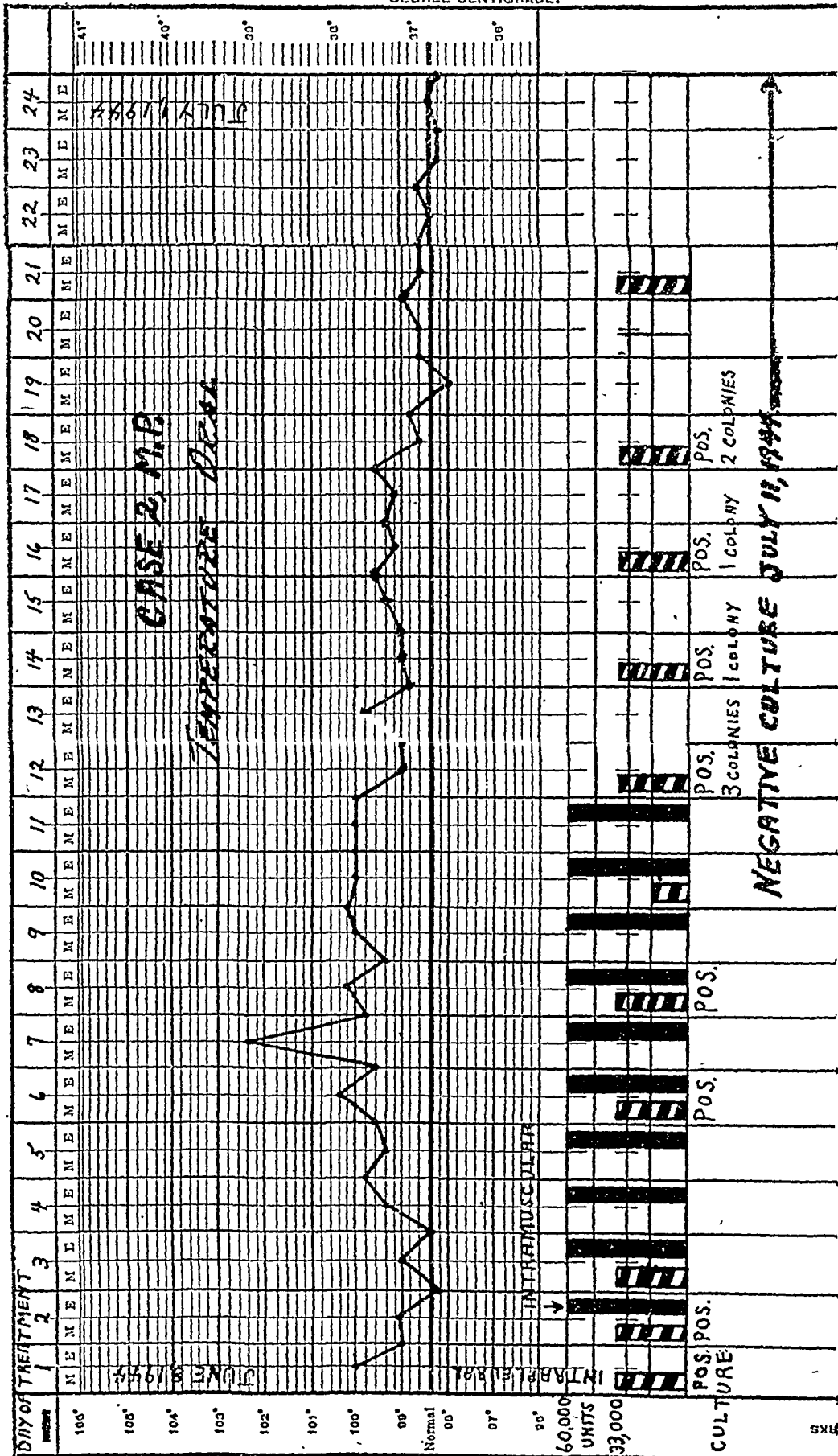


CHART 2

rally, after the empyema space had been aspirated as completely as possible of pus. The pus was again found positive for *Staphylococcus aureus* by culture. Since all subsequent attempts to needle the empyema space were unsuccessful, the patient received no additional intrapleural penicillin and no further aspirations of pus. She continued for the next fourteen days to receive penicillin intramuscularly, at the rate of 60,000 units daily in six doses per day, for an overall total of 890,000 units intramuscularly and of 30,000 units intrapleurally. Temperature response is shown in chart 1. By the ninth day of treatment patient was afebrile and asymptomatic except for weakness and anorexia. She was discharged back to Laurel Heights on March 5, 1944, eighteen days after the beginning of treatment.

On return to the sanatorium, the patient's X-ray film showed a small pneumothorax pocket over the left apex containing only a minimal amount of fluid. Careful questioning elicited the fact that, beginning the day after the one intrapleural injection of penicillin, the patient had expectorated creamy pus for a period of approximately two days, a symptom not previously reported. There was no expectoration either before or after this episode. It was concluded, therefore, that the patient had almost certainly developed, at the time, a temporarily patent bronchopleural fistula through which the empyema had drained.

On a continued rest regimen the patient improved steadily in strength and was discharged home on May 16, 1944, with arrested pulmonary disease and with a very small residual hydropneumothorax pocket. This was found completely absorbed on reexamination three months later (figure 1B) at which time obliteration of the pleural space appeared complete. The patient has continued to be asymptomatic, with normal temperature.

*Case 2:* M. P., a white woman aged 28, was admitted to Laurel Heights on January 15, 1942. Left pneumothorax was induced on March 5, 1942, when her moderately advanced tuberculosis in the left lung showed progression and questionable cavitation. Though the pneumothorax soon appeared anatomically satisfactory, consistent sputum conversion was not obtained until June, 1943. The patient was discharged as arrested in May, 1944. During residence the pneumothorax had twice been complicated by small transient clear effusions negative for both tubercle bacilli and pyogenic organisms on smear and culture. These had not been troublesome and no pleural fluid was present at discharge.

On May 18, 1944, sixteen days after discharge and two days following her first pneumothorax refill at another clinic, the patient developed severe pain in the chest, followed by dyspnea and fever to 103°F. A diagnosis of mixed tuberculous and staphylococcus empyema was made on the basis of a new X-ray film and thoracocentesis of pus, positive for both organisms. She was put to bed and treated by thoracocentesis pending transfer back to Laurel Heights.

On her return to Laurel Heights on June 5, 1944 (figure 2A) the patient was obviously toxemic and dyspneic with temperature of 102.6°F. Thoracocentesis produced 500 cc. of pea-soup like pus, positive by smear and culture for hemolytic *Staphylococcus aureus*.

The patient was readmitted and treatment was started on June 8, 1944, with the injection of penicillin intramuscularly and intrapleurally on a schedule indicated in chart 2. Each intrapleural injection was immediately preceded by the aspiration of all the pus which could be obtained. The temperature response and results of repeated blood agar plate cultures of the aspirated pleural exudate are also shown in chart 2. This exudate continued to be purulent up to the twenty-first day of treatment. X-ray film and fluoroscopy at this time indicated that some pleural fluid was still present, but several aspira-

tions attempted subsequently failed to produce any. Finally on July 11, 1944, 4 cc. of thin clear and slightly blood-tinged fluid were obtained, negative on culture. No further aspirations were attempted.

Soon after the beginning of penicillin treatment and many days before the temperature returned completely to normal, the patient began to feel well and her clinical status has improved steadily ever since. An X-ray film of August 29, 1944 (figure 2B) showed that absorption of pleural fluid and air was complete, and the status of residual parenchymal disease in the expanded left lung appeared satisfactory. A relatively thin peripheral pleuritic density, presumably thickened pleura, remained.

#### DISCUSSION

Though tubercle bacilli were never recovered from the pleural exudate in case 1, the acute and culturally sterile effusion for which the patient was being treated when the pyogenic empyema occurred was typical in onset, course and character of an acute tuberculous effusion complicating therapeutic pneumothorax. It is probable, therefore, that here, as in case 2, we were actually dealing with a mixed tuberculous and pyogenic empyema. It is interesting to note that, with penicillin continued intramuscularly, case 1 made a satisfactory response even though technical difficulties prevented the administration of more than one intrapleural dose.

Two cases obviously do not constitute a definitive series. Nevertheless, the excellent and prompt response of these 2 patients to penicillin therapy, together with the known effectiveness of penicillin in other infections caused by susceptible organisms, strongly suggests that we may, at last, have a really effective drug for the medical treatment of this dreaded complication of pneumothorax, at least in those cases in which expansion of the collapsed lung and obliteration of the pleural space is feasible. This does not imply that need for surgery is necessarily eliminated, even when the pyogenic pleural infection complicating a pneumothorax is successfully treated medically. Thoracoplasty may be needed because of underlying pulmonary disease inadequately controlled by the pneumothorax, because of a residual tuberculous empyema, or because obliteration of the pleural space cannot otherwise be completed. The potential superiority of penicillin therapy over preliminary tube drainage as a means of bringing such cases to thoracoplasty promptly, safely and in good condition is, however, apparent.

#### SUMMARY

Two cases are reported in which a staphylococcus empyema complicating therapeutic pneumothorax was cured, with obliteration of the empyema space, by penicillin therapy.

#### SUMARIO

Comunicanse dos casos en que la penicilinoterapia curó un empiema estafilocócico que complicaba un neumotórax terapéutico, eliminando la cavidad empiemática.

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# MILIARY TUBERCULOSIS OF THE LIVER<sup>1</sup>

GEORGE A. WOLF, JR. AND CURTIS M. FLORY

Miliary tuberculosis of the liver is not a commonly recognized clinical entity. Warthin in 1908 (1) reported 2 cases of pylephlebogenous miliary tuberculosis of the liver originally diagnosed as Weil's disease and typhoid fever. He emphasized that the clinical picture was that of an acute typhoidal state associated with jaundice and he prophesied that awareness of this diagnostic possibility would lead to more frequent recognition of the condition. Both of his cases occurred in middle aged men. The duration of the illness in each case was three weeks and the state of the patient was characterized by chills, fever, marked icterus, headache, muscle pains and delirium. The liver and spleen were palpable but physical findings other than those of a severe acute febrile illness were absent. Postmortem examination in each case revealed the erosion of radicals of the portal vein by caseous abdominal lymph nodes with direct transmission of infected material to the liver via the portal vein. In one case tubercles were not organs of the body and in the other case a few young tubercles were found in the found in other lungs. The intensity of the search for other tubercles or caseous foci in other organs is not clearly indicated.

In 1930 Randolph (2) reviewed the literature and reported a case of acute miliary tuberculosis of the liver which resembled clinically the cases reported by Warthin. The patient was in the sixth decade and had an illness of fourteen days' duration. Chills and continued fever were prominent symptoms. The spleen was enlarged and the liver suddenly increased in size between the ninth and twelfth days of the illness. A moderate anemia was present. There was no icterus. At postmortem gross examination of the liver revealed miliary tubercles in a similar stage of development. The primary site of the infection was not noted nor were other organs examined microscopically for the presence of tubercles.

It is the purpose of this paper to report a case of primary intestinal tuberculosis with massive miliary spread to the liver and generalized miliary tuberculosis which manifested itself as an acute typhoidal state.

## CASE REPORT

The patient was a 16 year old white, American, school girl who was admitted to the New York Hospital on December 17, 1943, complaining of chills and fever of six weeks' duration. Eight weeks prior to admission the patient had a mild sore throat which cleared up in three days. Two weeks later she noted the onset of general malaise, chills and fever as high as 102°F. Pus was said to have been found in the urine, and the patient was kept in bed for three weeks during which time she ran a low grade fever. Three weeks before admission she again developed chills and her temperature rose to 104°F. She was admitted to another hospital and thoroughly studied. The only positive findings included a marked anemia and a slight leucocytosis. The patient continued to have daily chills and fever and

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at the end of a three-week period she was transferred to the New York Hospital. No history of tuberculosis in her family could be elicited.

The physical examination revealed a temperature of 39.3°C., pulse 110 per minute, respirations 26 per minute and a blood pressure of 112/76. The patient was very thin and weak. She appeared pale and acutely ill. She was not jaundiced. The skin was clear. The fundi revealed no miliary tubercles. The head and neck were not remarkable except for pallor of the mucous membranes. The lungs were resonant throughout and a few fine râles were heard at the right base on deep inspiration. The heart was not enlarged. The rate was rapid and there was an apical diastolic gallop. P2 was accentuated but there were no murmurs. The abdomen was moderately distended. There was slight tenderness in the right upper quadrant. The liver was palpable 5 cm. below the right costal margin. The spleen was not felt and there was no tenderness in the costovertebral angle. The remainder of the physical examination was not remarkable.

Laboratory examination showed the urine to be acid and to contain a trace of albumin. There were a few red cells and occasional white blood cells in the centrifuged catheterized specimen. Urine culture for tubercle bacilli was positive after fifty-seven days of incubation. There were 8 g. per 100 cc. of hemoglobin in the blood and 3 million red blood cells. The leucocyte count was 6,900 with 3 lymphocytes, 3 monocytes, 47 mature polymorphonuclear leucocytes and 47 immature forms. The Mazzini test was negative. The blood urea nitrogen was 16 mg. per cent. The serum proteins were 4.5 g. per cent with 2.1 g. of albumin and 2.4 g. of globulin. The icteric index was 7 units. The stools were brown in color and contained no blood according to the guaiac test. The brucella and Widal agglutinations were negative. The prothrombin level by the Warner, Brinkhouse, Smith method was only 11 per cent of normal. The blood cultures on the usual media were negative but blood cultures taken on Petraghani's medium were found positive for tubercle bacilli after eight weeks. Rabbits and guinea pigs were inoculated intravenously with this strain of tubercle bacilli.

Two rabbits received 0.01 mg. of the strain of tubercle bacilli intravenously and one hundred days later showed no evidence of tuberculosis on inspection of the kidneys, lungs, peritoneum, liver. Guinea pigs injected subcutaneously with about 2,000 organisms showed in twenty-five days massive involvement of the liver, lymph nodes, spleen and lungs.

The patient was treated with sulfadiazine; this had no effect on her temperature which remained at about 40°C. On the third hospital day, because of the palpable liver and tenderness in the right upper quadrant, the patient was operated upon. Digital exploration of the peritoneal cavity in the right lower quadrant revealed a large mass of matted lymph nodes in the root of the mesentery. The operative wound was closed without further exploration and the patient was returned to the pavilion. She expired four hours later.

Prior to operation, miliary tuberculosis was considered because of the age of the patient, appearance of severe, rapidly progressive infection without demonstration of an obvious etiological agent with the usual clinical tests. The enlarged liver was unexplained. Others subsequently felt, because of the enlarged liver, that a pyelephlebitis was most probable. Because of this the patient was explored and, when the large masses of matted nodes were felt without obvious miliary nodules on the area of peritoneum explored, it was concluded that the patient had Hodgkin's disease or some related disorder.

## AUTOPSY REPORT

*(Autopsy No. 1195)*

*Macroscopic examination:* The body was that of a moderately emaciated young white woman. The skin was pale and not icteric. There was a recent unhealed surgical incision in the right lower quadrant of the abdomen. The cervical, axillary and inguinal lymph nodes were not enlarged. The peritoneal cavity contained 1,100 cc. of cloudy fluid. The liver was greatly enlarged; its rounded margin extended eight cm. below the right costal border. On its capsular surface were many minute gray-white nodules, and in the liver tissue beneath were innumerable gray-yellow nodules measuring up to 2 mm. in diameter. The spleen was moderately enlarged. The stomach and small intestine were not distended. The terminal 10 cm. of the ileum and the first 3 cm. of the cecum were thickened, firm and covered with many gray-yellow nodules which averaged one mm. in diameter. The lymph nodes between the terminal ileum and the pancreas were greatly enlarged, some measuring as much as 3 cm. in diameter. The larger nodes were semi-fluctuant. The nodes about the head of the pancreas were moderately enlarged and firm. The colon and internal generative organs were normal.

The esophagus, stomach, duodenum and jejunum were normal. In the ileum, at a point 18 cm. from the ileocecal valve, the Peyer's patches were ulcerated. This ulceration was more wide-spread, lower down in the ileum, and in the terminal 10 cm. of the ileum, the entire mucosal surface was ulcerated and replaced by a rough shaggy layer of gray-white exudate. The muscular and serosal layers were thick and firm and measured in some places as much as 8 mm. in thickness. They contained many gray nodules about one mm. in diameter. The serosal surface of this portion of the ileum was covered with very small yellow-gray nodules. This hyperplastic and ulcerative process extended into the proximal three cm. of the cecum. Although the ileocecal valve was ulcerated, it was not obstructed. There were no ulcers in the colon beyond the cecum. The ileocecal region is shown in figure 1.

The nodes lying between the terminal ileum and the pancreas were greatly enlarged, measuring up to 3 cm. in diameter. They were semi-fluctuant and contained a green-gray semi-liquid material. Together these nodes formed a mass which measured 14 by 6 by 4 cm. After fixation, the cut-surfaces of these nodes were firm, white and caseous (figure 2). The nodes about the pancreas and hilum of the liver were enlarged but their cut-surfaces were firm. The abdominal periaortic nodes were moderately enlarged; their cut-surfaces were caseous. The peribronchial and peritracheal nodes were slightly enlarged; their surfaces revealed no areas of caseation. The cervical lymph nodes were not enlarged.

The portal vein and its radicals were opened and no areas of caseous ulceration found on gross examination.

The liver weighed 3,650 g. and was about three times its normal size. On its surface were many miliary, gray-white nodules, and in the liver tissue itself tremendous numbers of gray-yellow nodules (figure 3). These nodules measured up to 2 mm. in diameter and were so numerous that it was estimated that they composed between a fourth and a fifth of the liver substance. They were evenly distributed between the right and left lobes. The hepatic and portal veins within the liver were normal.

The spleen weighed 310 g. In its capsule were a few miliary gray-white nodules and its cut-surfaces revealed many similar nodules. These were, however, smaller and less numerous than those in the liver.

On the pleura and the cut-surfaces of the lungs were many minute gray-white nodules.





FIG. 1. Tuberculosis of terminal ileum and cecum. The ulceration of the mucosal surface and the thickening of the wall of the intestine are clearly shown.

FIG. 2. Tuberculosis of mesenteric lymph nodes. This mass of lymph nodes as found between the terminal ileum, which is visible in the lower portion of the photograph, and the head of the pancreas. The nodes have been split open to expose their caseous surfaces.

FIG. 3. Miliary tuberculosis of the liver. This is a cut-surface of the liver.

FIG. 4. Photomicrograph of miliary tubercles in liver, showing a cluster of the tubercles; their large size is evident.

These nodules were also smaller and less numerous than those in the liver. In the subpleural area of the left upper lobe was a 3 mm. rounded caseous nodule. The peribronchial and peritracheal lymph nodes were slightly enlarged, but contained no areas of caseation.

In each kidney were scattered miliary nodules and several wedge-shaped soft white areas extending from the outer cortex into the lower medulla. These were fairly well demarcated and had the appearance of caseous infarcts. The largest measured 5 by 5 by 15 mm. The renal pelvis, the ureters and urinary bladder were normal.

The heart, great vessels, bile ducts and gallbladder, pancreas, adrenals, female generative organs, larynx, pharynx and trachea were not remarkable. The brain could not be examined.

*Microscopic examination:* The entire wall of the ileum was thickened. Only a few fragments of the epithelium remained and most of the mucosal surface had been replaced by amorphous caseous material surrounded by a few macrophages. The submucosa was greatly thickened and contained a large number of areas of caseation surrounded by a few epithelioid cells, a few fibrocytes and no giant cells. There were many more of these caseous tubercles in the muscularis and the serosal coat of the intestine. When this section was stained for acid-fast organisms large numbers of bacteria with the appearance of tubercle bacilli were found in the areas of caseation and in the surrounding epithelioid cells.

The disease process in the cecum was similar to that in the terminal ileum.

The lymph nodes near the terminal ileum were replaced by large masses of caseous necrosis surrounded by a thin wall of epithelioid cells. Acid-fast stains revealed many tubercle bacilli in and around these masses.

Many venules were seen about the areas of caseation, and in many places the walls of these vessels were involved by the inflammatory process. In the acid-fast stains tubercle bacilli could be seen in the partially necrotic walls of these venules.

The peripancreatic lymph nodes contained many miliary tubercles.

In every section of the liver were many large, caseous miliary tubercles. The cellular reaction about the caseous material was scanty. The tubercles were most numerous in the portal areas. Figure 4 illustrates the process in the liver. Acid-fast stains revealed large numbers of tubercle bacilli in these areas of caseation.

The pulmonary tissue contained many small miliary tubercles. The tracheobronchial lymph nodes contained scattered miliary tubercles.

An occasional miliary tubercle was present in the cortex of the kidneys. The white, wedge-shaped areas seen on gross examination were areas of caseous tuberculosis.

A few miliary tubercles were found in the bone marrow and spleen. The other organs contained no tubercles.

*Anatomical diagnosis:* Primary ulcerative tuberculosis of the terminal ileum and cecum.

Caseous tuberculosis of the mesenteric and periaortic lymph nodes.

Massive miliary tuberculosis of the liver, probably pylephlegmogenous in origin; miliary tuberculosis of the lungs, spleen, kidneys and bone marrow.

Caseous tuberculosis of kidneys (tuberculous "infarcts").

Caseous miliary tubercles in lung.

#### DISCUSSION

The cultures for tubercle bacillus in blood and urine were not reported until after the death of the patient and there was no proof during life that the disease was tuberculous. The possibility of liver abscess of septic origin was considered

and it was on the basis of this suspicion that surgical exploration was undertaken. It is interesting that inspection of the abdominal cavity at the operating table disclosed the enlarged lymph nodes but did not reveal recognizable tubercles. It was indeed the impression of the experienced surgeon that the lesions might be due to Hodgkin's disease.

Tubercle bacillema is infrequently found in tuberculosis, possibly because it is rarely searched for. Clough (3) and Shapiro (4) using a special cultural method demonstrated tubercle bacilli in the blood of 4.2 and 6.7 per cent of unselected cases of tuberculosis, and the former demonstrated a bacteremia in 66 per cent of cases of miliary tuberculosis. Petersen and Lederman (5) in 1934 were unable to confirm these findings using the same cultural technique. The literature on this subject is extensive. There was no difficulty in demonstrating tubercle bacilli in the blood of the patient reported in this paper.

Reichle (6) in 1936 reviewed the subject of primary intestinal tuberculosis and reported 2 cases. His figures on the incidence of this type of tuberculosis in various parts of the world are of interest. The incidence of active and healed primary intestinal tuberculosis among cases of tuberculosis in England is given as 34.2 per cent. The incidence in New York City is given as 4.3 per cent. Crohn and Yarnis (7), in 1940, carefully studied the surgical pathological material and 4,800 autopsies at Mount Sinai Hospital in New York City and were able to find only one proved case of primary intestinal tuberculosis, although they made a presumptive diagnosis in 7 surgical specimens. They point out that the older literature may have included cases of what are now recognized as regional enteritis. In areas where the bovine organism is present primary intestinal tuberculosis is more common. Brown and Sampson (8) quote a series of 28 cases of which 25 were infected by the bovine strain. A rather complete review of the literature concerning primary intestinal tuberculosis is included in a report of 2 cases by Bockus, Tumen and Kornblum (9).

It was felt that the findings justified calling the ileocecal lesion primary intestinal tuberculosis because no other primary complex was found, and the lesions in the ileum and cecum were typical of those described in primary intestinal tuberculosis (6). The small caseous focus in the lung was probably of the same age as the caseous nodules in the kidneys, and both probably resulted from a small blood-stream dissemination of tubercle bacilli which occurred some weeks before the final massive miliary spread. If this caseous nodule in the lung were a primary tubercle, one would also expect to find caseation in the peribronchial lymph nodes; this was not the case. There was no evidence of healed primary tuberculosis in the chest roentgenogram.

The density of the miliary tubercles in the liver was so great in comparison with that seen in most cases of miliary tuberculosis that it seems certain that the seeding of tubercle bacilli was through the portal vein. In all other cases of miliary tuberculosis we have studied there have been relatively few miliary tubercles in the liver, and these have not constituted an appreciable part of the liver substance. In this case, however, a fourth or a fifth of the liver tissue was replaced by miliary tubercles, all of which were of a large size. Ulceration

of a caseous node into a branch of the portal vein was not actually demonstrated. Microscopic examination of small portal vein radicles in and about the caseous abdominal nodes revealed many instances of destruction of the walls of the vessels by the inflammatory process. Tubercle bacilli may have gained access to the portal blood-stream through these small foci. It is possible, however, that somewhere in the huge mass of caseous abdominal lymph nodes gross ulceration had occurred into a large branch of the portal vein and given rise to the massive miliary tuberculosis of the liver.

Tuberculosis of the intestine is not at all uncommon in patients with other forms of tuberculosis. Crawford and Sawyer (10) in 1934 in 1,400 autopsies on tuberculous patients found it in 68.8 per cent, and Williams (11) in 1938 reported its incidence in 242 autopsies as 69 per cent. Massive spread of the infection through the portal system to the liver, however, usually does not occur. Miliary tubercles in the liver may be found in 50 to 80 per cent of cases of pulmonary tuberculosis according to Morris (12), but the syndrome of fever, chills and enlarged liver with or without jaundice as described by Warthin (1), Randolph (2) and in the present report is rare. This syndrome should be attributed to massive miliary tuberculosis of the liver resulting in these instances from pylephlebogenous spread of the infection.

#### SUMMARY

A 16 year old female patient had an illness characterized by chills, fever, prostration and anemia associated with massive enlargement of the liver. There was diminished liver function as evidenced by an extremely low prothrombin level in the blood. Blood cultures were positive for tubercle bacilli. Death occurred six weeks after the onset of the disease.

Postmortem examination revealed primary ulcerative tuberculosis of the ileocecal region, caseous tuberculosis of the abdominal lymph nodes, massive miliary tuberculosis of the liver and scattered miliary tubercles elsewhere in the body.

It is believed that the extensive involvement of the liver was caused by pylephlebogenous spread of the infection to the liver.

#### SUMARIO

Una enferma de 60 años tuvo una enfermedad caracterizada por escalofríos, fiebre, agotamiento y anemia asociadas a hepatomegalia masiva. La hipofunción del hígado se traducía por una hipoprotrombinemia excesiva. Los hemocultivos resultaron positivos en cuanto a bacilos tuberculosos. La muerte sobrevino a las 6 semanas de la iniciación de la dolencia.

La autopsia reveló tuberculosis ulcerada primaria de la región ileocecal, tuberculosis caseosa de los ganglios linfáticos abdominales, granulía masiva del hígado y tubérculos miliares esparcidos en otras partes del cuerpo.

Según parece, la extensa invasión hepática se debió a propagación pileflebógena de la infección al hígado.

*Acknowledgment*

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# THE BLOOD IODINE IN PULMONARY TUBERCULOSIS<sup>1, 2</sup>

KARL P. KLASSEN, ELSIE L. RILEY AND GEORGE M. CURTIS

The similarity of certain symptoms, occurring both in pulmonary tuberculosis and hyperthyroidism, is well known. Thus, the presence of tachycardia, nervousness and weight loss has led to a common belief that there is an associated hyperfunction of the thyroid gland in active pulmonary tuberculosis. Fishberg (1) suggests that there is a transitory hyperthyroidism in the early stages of pulmonary tuberculosis. Coulaud (2) found evidence of thyroid hyperplasia in patients who died of acute pulmonary tuberculosis. Hashimoto (3) and also Ishimaru (4) demonstrated thyroid hyperfunction in experimental animals infected with tuberculosis, while Webb (5) was able to produce thyroid hypertrophy in tuberculous guinea pigs. Experimental work by Piazza (6), Labbe, Vitry and Giraud (7) suggests an increased thyroid function in pulmonary tuberculosis. These investigators found an increase in the thyroid iodine in patients who had died of pulmonary tuberculosis.

Basal metabolic rate determinations in patients with pulmonary tuberculosis by a number of investigators (8, 9, 10, 11) failed to reveal an increased rate. In patients with chronic pulmonary tuberculosis Coulaud (2) found thyroid atrophy and sclerosis, while Rose and Hopkins (12) were unable to demonstrate histological evidence of hyperthyroidism in the thyroid tissue of such patients.

In recent years the estimation of the blood iodine concentration has become of definite value in the diagnosis of hyperthyroidism. The majority of patients with untreated hyperthyroidism present an increased blood iodine (13). Anthes (14), Veil and Sturm (15) were the first to use this diagnostic aid in their study of the thyroid function in patients with pulmonary tuberculosis; however they found no increase in the blood iodine level. In a previous publication (16) we presented the results of our investigation of the urinary excretion of iodine in patients with pulmonary tuberculosis. We were unable to demonstrate an increased urinary loss of iodine in these patients, as is found in patients with clinical hyperthyroidism (17).

It appears then, that there is still a wide diversity of opinion as to the activity of the thyroid gland in patients with active pulmonary tuberculosis. Further studies were indicated in order to clarify this problem. We were presented with an excellent opportunity to study the blood iodine in a large number of patients with pulmonary tuberculosis in a county tuberculosis hospital. The present report deals with the results of this study.

## METHODS

The patients used in this investigation were unselected, except that all those having had iodine medication in any form were excluded. None had palpable

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goitres. The ages of the patients varied from 15 to 69 years; 69 were male and 46 female. The extent of the tuberculous lesion was determined by physical examination, X-ray studies of the lungs, sputum analyses and blood studies. Of all the patients only 12 had a slight fever during the period of study. The diet of the patients was low in iodine, as is found in the food of central Ohio. No iodized salt was used in the preparation of meals. The patients had spent

TABLE 1  
*The blood iodine in patients with pulmonary tuberculosis*

	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED
Number of cases.....	6	19	90
Low and high limits of blood iodine, mcg. per cent.....	3.2-4.8	2.2-6.4	2.0-8.3
Average blood iodine, mcg. per cent.....	3.7	3.9	3.9

A Comparison of the Ranges of the Blood Iodine Concentration  
in Patients with Pulmonary Tuberculosis.

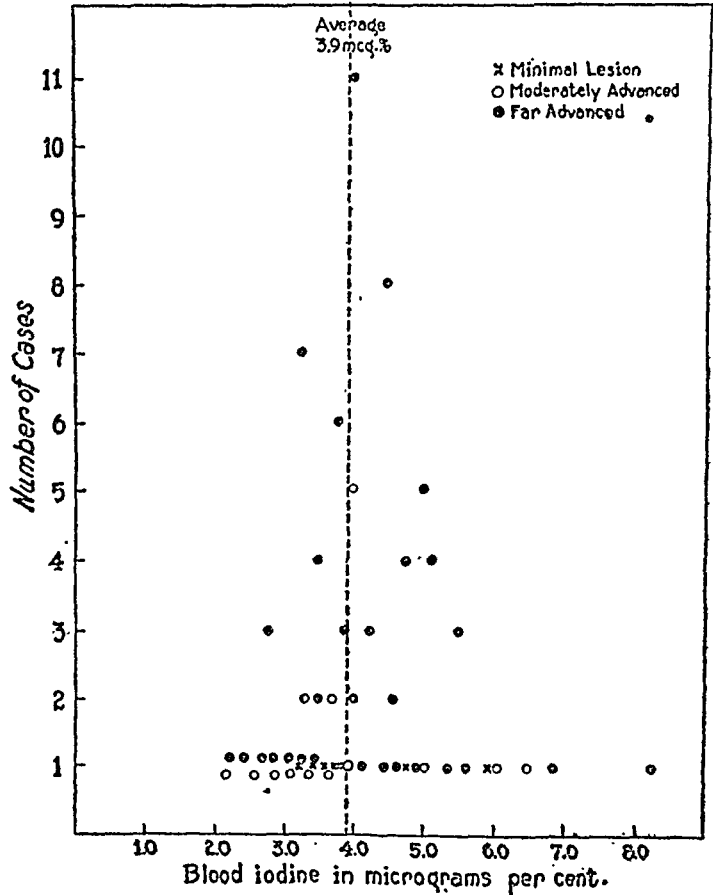


FIG. 1

at least two weeks in the hospital before the blood for the iodine determination was drawn; 25 cc. of oxalated blood was used for the iodine analysis by the micromethod used in our laboratory (18).

#### OBSERVATIONS

The blood iodine concentration in three groups of patients with pulmonary tuberculosis is presented in table 1 and figure 1. Only 6 patients had minimal, active lesions, while the majority had far advanced pulmonary tuberculosis. The average blood iodine concentration in the 6 patients with minimal lesions was 3.7 micrograms per cent, which is within the normal range of 3 to 5.0 of micrograms per cent for this region and by our method of iodine determination. One of these patients had a daily temperature elevation to 99.8° F. Her blood iodine concentration was 4.8 micrograms per cent. The temperature of the other patients was normal.

In the 19 patients with moderately advanced tuberculosis there was a greater individual variation in the low and high limits of blood iodine, but the majority of the blood iodine determinations fell within the range of normal, with an average value of 3.9 micrograms per cent. One patient, with a temperature elevation of 99.2° F., had a blood iodine value of 2.9 micrograms per cent. All other patients were afebrile.

The largest group of patients had advanced pulmonary tuberculosis. There was a great individual variation in the blood iodine concentration, however, the average blood iodine was 3.9 micrograms per cent, which is normal. Ten patients had fever, with the highest rise to 101.2° F. The average blood iodine in these 10 patients was 4.0 micrograms per cent.

#### DISCUSSION

The conditions under which the patients with pulmonary tuberculosis were studied were in every respect the same as present in the large group of patients with hyperthyroidism studied in and reported previously from our clinic (13). The iodine intake, an important factor in determining the iodine level in the blood, was the same, and was somewhat lower than found in other geographical regions of the United States. No medication containing iodine was used. The finding of a normal blood iodine level in all these patients clearly indicates that there is no hyperthyroidism associated with tuberculosis of the lung, in its various stages of progress.

It has been found in our clinic that the increased blood iodine concentration is particularly marked in the early stages of hyperthyroidism, before the iodine of the organism has been depleted. Such depletion of the available body iodine may occur in patients with hyperthyroidism of long standing. The available iodine is gradually lost through the various channels of iodine excretion, as the kidneys, intestines, lungs and skin. However, the number of patients with hyperthyroidism and normal blood iodine is relatively small.



An increased thyroid activity in patients with pulmonary tuberculosis should particularly be marked in the patients with minimal pulmonary lesions, where the disease is of relatively short duration, and would be reflected in an increased blood iodine level. This was not the case. In all patients with minimal tuberculosis the blood iodine was well within the normal range.

The patients with moderately and far advanced pulmonary tuberculosis also had a normal blood iodine concentration. No correlation could be found between the duration of the disease and the blood iodine level. In several patients the disease was rapidly progressive and had been present for only a few months, while others had been ill for a number of years. In the first group thyroid hyperactivity would certainly have been reflected by a high blood iodine level, while in the latter and larger group there should have occurred a gradual but definite depletion of the available body iodine, since the intake of iodine was comparatively low. In our previous report on the excretion of iodine in the urine of patients with pulmonary tuberculosis we were unable to demonstrate an increased loss of iodine. None of the patients with both acute, rapidly progressive and chronic moderately and far advanced pulmonary tuberculosis showed an appreciable deviation of the blood iodine level from the normal.

The symptoms of pulmonary tuberculosis, simulating those of thyrotoxicosis appear not to be due to thyroid overactivity, but rather to the complex changes in the entire body metabolic processes produced by this disease. Fever increases oxygen consumption and produces elevation of the basal metabolic rate; however, the thyroid gland does not appear to be responsible for this elevation, as the blood iodine is not elevated. From our blood iodine determinations in the 115 patients with pulmonary tuberculosis, we were unable to demonstrate an increased activity of the thyroid gland.

#### SUMMARY

In 115 patients with active pulmonary tuberculosis the blood iodine concentration was normal. It varied from 2.0 to 8.3 micrograms per cent with an average value of 3.9 micrograms per cent. The extent of the pulmonary lesion, duration of illness and severity of symptoms did not influence the blood iodine concentration.

The present study indicates that there is no demonstrable hyperthyroidism associated with active pulmonary tuberculosis.

#### SUMARIO

En 115 enfermos con tuberculosis pulmonar activa, la yodemia resultó normal, variando de 2.0 a 8.3 microgramos por ciento y promediando 3.9 microgramos por ciento. La extensión de la lesión pulmonar, la duración de la enfermedad y la gravedad de los síntomas, no afectaron la concentración del yodo en la sangre.

El estudio actual demuestra que no existe hipertiroidismo demostrable asociado a la tuberculosis pulmonar activa.

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## IN VITRO PHAGOCYTOSIS<sup>1, 2</sup>

### *In Vitro* Phagocytic Cell Sensitivity in Normal, Tuberculo-anaphylactic, Tuberculo-allergic and Tuberculous Guinea Pigs

H. J. CORPER, MAURICE L. COHN AND RAY E. STONER

Although *in vitro* cellular observations may frequently be misleading for *in vivo* interpretations, cautious correlative evaluation at times has led to invaluable findings which have been the basis for new conceptions in biology and medicine or have even revolutionized the entire fundamental reasoning applied to certain branches of the biological sciences. In the field of tuberculosis, it has been particularly important not to avoid or short cut certain modes of scientific procedure merely because they appeared redundant or of little importance for interpretation at the time. More careful and detailed observations have led to a reconsideration and clarification of older generally accepted conceptions as a result of such studies. Thus the views on the tuberculin liberation *in vivo* and tuberculinization, on the unity of tuberculo- (tuberculin) allergy and tuberculo-immunity, on the similarity of tuberculin anaphylaxis and tuberculo- (tuberculin) allergy, and on the unknown mechanism of the liberation of tuberculin *in vitro* have given way to more recent and proved concepts of these mechanisms (1, 2).

In earlier studies (3), it was shown that tuberculin (tuberculo-protein) sensitizes to anaphylaxis, provokes anaphylactic shock and allergic (tuberculin) intoxication, but does not sensitize to allergy (tuberculin or bacillary) nor specifically immunizes against virulent infection; while the viable tubercle bacillus sensitizes primarily to tuberculo-allergy and serves to immunize against virulent infection. While viable tubercle bacilli in small amounts produce tuberculo-allergic hypersensitiveness and specific tuberculo-immunity, heat-killed bacilli in saline do not accomplish this appreciably. However, the paraffin oils mixed with heat-killed bacilli markedly increase the ability of the latter to produce tuberculo-allergic hypersensitiveness (4). Appropriate injections of tuberculo-protein (natural Seitz filtrate) can desensitize or immunize against toxic local or general tuberculo-protein injections in tuberculo-allergic guinea pigs (5), but bacillary injections were not found to desensitize against bacillary allergy (6). However, appropriate injections of natural Seitz filtrate tuberculin (tuberculo-protein) did desensitize against anaphylactic tuberculo-protein intoxication (7).

With the foregoing information as a basis, it appeared desirable to study the isolated cell effects in order to obtain a better analysis of the existing conditions in tuberculous animals and man as compared with the normal. Since the effects appeared to be general cellular effects, especially as they pertained to phagocytic cells, and since the most accessible of such cells and those that had been used most successfully previously with acute pyogenic organisms as test

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<sup>2</sup> This study was aided by the Jacques Labarrere Fund for Tuberculosis Research.

were blood cells and bone marrow cells, these were used in the following *in vitro* experiments. The general techniques previously worked out by Welch and Hunter (8) for phagocytosis and by Schrek (9) for measuring cell toxicity were utilized. Welch and Hunter used *Staphylococcus aureus* as test organism and blood for phagocytic cells, while Schrek tested cell death by staining bone marrow cells, splenic cells and lymph node cells with eosin. In the following phagocytic studies, we used the human tubercle bacillus in fine suspension in addition to *Staphylococcus aureus*. These tubercle bacilli were stained with pararosaniline hydrochloride, as recommended by Yegian and associates (10, 11) and modified in order to avoid disruption of the phagocytic cells as a result of the use of the usual acid-fast staining technique. The following modified technique was used and proved satisfactory in our hands for determining phagocytosis of tubercle bacilli: The air dried smear was treated for one to two hours at incubator temperature (37° C.) with 0.3 per cent pararosaniline hydrochloride in 1 per cent phenol distilled water solution. Stronger phenol solutions destroyed the phagocytic cells. After thus staining the tubercle bacilli, the smear was decolorized by one-half minute contact with saturated boric acid in 70 per cent ethyl alcohol, after which the smear was carefully washed with tap water, air dried and counterstained for one minute with 1 cc. of a 0.5 per cent methylene blue solution in pure methyl alcohol which is then diluted by adding 1 cc. Tyrode's solution (NaCl 0.8, KCl 0.02, CaCl<sub>2</sub> 0.02, MgCl<sub>2</sub> 0.01, NaH<sub>2</sub>PO<sub>4</sub> 0.005, NaHCO<sub>3</sub> 0.1, and distilled water to 100 cc.), and contact continued for four minutes, after which the smear was washed carefully with tap water and allowed to dry in air for examination under oil immersion.

In order to note the effect of autolytic tuberculin (2) and natural Seitz filtrates of cultures of tubercle bacilli grown on a nonprotein synthetic medium (12) upon the phagocytosis of *Staphylococcus aureus* and human tubercle bacilli, as influenced by the source of the phagocytic cells from normal, allergically sensitized, tuberculin anaphylactically sensitized, tuberculous guinea pigs, or allergic or anaphylactic hypersensitive animals desensitized or immunized (treated) with tuberculo-protein or treated with dead tubercle bacilli, animals were thus prepared and their phagocytic cells tested with the results recorded in tables 1 and 2. In table 1 are recorded the results of the phagocytosis of *Staphylococcus aureus*.

It is to be noted from the results recorded in table 1 that tuberculo-protein contained in the Seitz filtrate (about 1 mg. per cc.) and autolytic tuberculin (tuberculo-protein) in concentrations as high as 50 mg. per cc., containing 10 per cent biologically active tuberculo-protein, does not appreciably affect the phagocytosis of *Staphylococcus aureus* by phagocytic cells obtained from normal guinea pigs; while the tuberculo-protein (tuberculin) reduces to about one-half the phagocytosis by cells obtained from tuberculo-allergic hypersensitive animals, anaphylactically hypersensitive guinea pigs or tuberculous guinea pigs. In all the allergic or anaphylactic tuberculo-hypersensitive animals which were treated with tuberculo-protein solutions (as Seitz filtrate) or with heat-killed bacilli, the phagocytosis of staphylococci was markedly depressed.

The foregoing experiment was repeated using viable human tubercle bacilli as test organism in place of the staphylococci with the results recorded in table 2.

TABLE 1

*Effect of natural Seitz filtrate and autolytic tuberculin on phagocytosis of Staphylococcus aureus*

TYPE OF ANIMAL TESTED	INTRACU- TANEOUS TUBERCU- LIN REACTION AT TIME OF TEST	AVERAGE NUMBER OF ORGAN- ISMS PHAGOCY- TIZED (CONTROL)	PER CENT NUMBER ORGANISMS PHAGOCYTIZED AS COMPARED WITH CONTROL AFTER CONTACT WITH			
			Natural Seitz† filtrate	Autolytic tuberculin‡		
				50 mg./ cc.	10 mg./ cc.	1 mg./ cc.
Control.....	0*	44	94	95	100	100
Immune prepared with 1 mg. avirulent hu- man tubercle bacilli subcutaneously.....	3	40	53	30	45	53
Immune and tuberculin desensitized with 1 mg. avirulent human tubercle bacilli sub- cutaneously and treated intravenously with natural Seitz filtrate.....	0	47	11	0	0	25
Immune and bacillary treated with 1 mg. avirulent human tubercle bacilli subcu- taneously and treated intravenously with heat-killed tubercle bacilli§.....	2	38	13	0	0	0
Tuberculo-allergic prepared with 1 mg. heat- killed tubercle bacilli in mineral oil subcu- taneously.....	3	41	78	45	56	69
Tuberculo-allergic and tuberculin desen- sitized with 1 mg. heat-killed tubercle bacilli in mineral oil subcutaneously and treated intravenously with natural Seitz filtrate.....	0	48	7	2	3	23
Tuberculo-allergic and bacillary treated with 1 mg. heat-killed tubercle bacilli in mineral oil subcutaneously and treated in- travenously with heat-killed tubercle bacilli§.....	1	43	0	0	0	0
Tuberculo-anaphylactic hypersensitive with 5 mg. tuberculo-protein as natural Seitz filtrate intravenously.....	0	46	77	54	67	67
Tuberculo-anaphylactic and desensitized with 5 mg. tuberculo-protein as natural Seitz filtrate intravenously and treated intravenously with natural Seitz filtrate...	0	42	0	0	0	41
Tuberculous (advanced disease).....	4	47	79	45	60	66
Tuberculous (slight disease).....	3	42	78	52	75	75

\* The tuberculin reaction is graded from 0 to 4, as is the standard custom.

† The Seitz filtrate used contained 1 mg. tuberculo-protein per cc.

‡ The autolytic tuberculin used contained 10 per cent biologically active tuberculo-protein.

§ In all cases where heat-killed bacilli were used they were obtained from young cultures (10 to 14 days) to avoid the presence of tuberculin as far as possible.

The results recorded in table 2 indicate that the phagocytosis of the tubercle bacilli is essentially affected in the same manner as that noted for the staphy-

lococci in spite of the fact that the allergic and anaphylactic hypersensitiveness in the guinea pig was specific against the tubercle bacillus and its *in vitro* product,

TABLE 2

*Effect of natural Seitz filtrate and autolytic tuberculin on phagocytosis of tubercle bacilli*

TYPE OF ANIMAL TESTED	INTRACU- TANEOUS TUBERCU- LIN REACTION AT TIME OF TEST	AVERAGE NUMBER OF BACILLI PHAGOCY- TIZED (CONTROL)	PER CENT NUMBER OF BACILLI PHAGOCYTIZED AS COMPARED WITH CONTROL AFTER CONTACT WITH			
			Natural Seitz† filtrate	Autolytic tuberculin‡		
				50 mg./ cc.	10 mg./ cc.	1 mg./ cc.
Control.....	0*	23	84	56	95	100
Immune prepared with 1 mg. avirulent hu- man tubercle bacilli subcutaneously.....	3	23	62	40	43	65
Immune and immune desensitized with 1 mg. avirulent human tubercle bacilli subcu- taneously and treated intravenously with natural Seitz filtrate.....	0	24	15	2	14	58
Immune and bacillary treated with 1 mg. avirulent human tubercle bacilli subcu- taneously and treated intravenously with heat-killed tubercle bacilli§.....	2	24	69	12	31	54
Tuberculo-allergic prepared with 1 mg. heat- killed tubercle bacilli in mineral oil subcu- taneously.....	3	23	86	45	50	58
Tuberculo-allergic and tuberculin desen- sitized with 1 mg. heat-killed tubercle bacilli in mineral oil subcutaneously and treated intravenously with natural Seitz filtrate.....	0	24	36	12	20	57
Tuberculo-allergic and bacillary treated with 1 mg. heat-killed tubercle bacilli in mineral oil subcutaneously and treated intravenously with heat-killed tubercle bacilli§.....	1	28	4	4	4	4
Tuberculo-anaphylactic hypersensitive with 5 mg. tuberculo-protein as natural Seitz filtrate intravenously.....	0	22	48	29	54	68
Tuberculo-anaphylactic and desensitized with 5 mg. tuberculo-protein as natural Seitz filtrate intravenously and treated intravenously with natural Seitz filtrate...	0	29	0	0	0	55
Tuberculous (advanced disease).....	4	27	67	41	48	85
Tuberculous (slight disease).....	3	30	73	40	47	67

\* The tuberculin reaction is graded as customarily from 0 to 4.

† The Seitz filtrate contained 1 mg. tuberculo-protein per cc.

‡ The autolytic tuberculin contained 10 per cent biologically active tuberculo-protein.

§ All heat-killed bacilli were obtained from young cultures (10 to 14 days) as free from tuberculin as possible.

tuberculin. There was an appreciable reduction of the phagocytosis of the tubercle bacilli in the presence of tuberculin (tuberculo-protein) by phagocytes

obtained from the allergic hypersensitive, anaphylactic hypersensitive and tuberculous guinea pigs which became more pronounced if these animals had been

TABLE 3

*Effect of natural Seitz filtrate and autolytic tuberculin on bone marrow cells*

TYPE OF ANIMAL TESTED	INTRACU- TANEOUS TUBERCU- LIN REACTION AT TIME OF TEST	PER CENT STAINED CELLS AFTER CONTACT WITH				
		Control	Natural Seitz† filtrate	Autolytic tuberculin‡		
				50 mg./ cc.	10 mg./ cc.	1 mg./ cc.
Control.....	0*	9	19	25	15	11
Immune prepared with 1 mg. avirulent human tubercle bacilli subcutaneously.....	3	9	14	19	13	13
Immune and tuberculin desensitized with 1 mg. avirulent human tubercle bacilli subcutaneously and treated intravenously with natural Seitz filtrate.....	0	16	17	24	22	17
Immune and bacillary treated with 1 mg. avirulent human tubercle bacilli subcutaneously and treated intravenously with heat-killed bacilli§.....	2	10	12	18	12	12
Tuberculoallergic prepared with 1 mg. heat-killed tubercle bacilli in mineral oil subcutaneously.....	3	12	14	15	13	11
Tuberculo-allergic and tuberculin desensitized with 1 mg. heat-killed tubercle bacilli in mineral oil subcutaneously and treated intravenously with natural Seitz filtrate.....	0	18	19	22	20	22
Tuberculo-allergic and bacillary treated with 1 mg. heat-killed tubercle bacilli in mineral oil subcutaneously and treated intravenously with heat-killed tubercle bacilli§....	1	11	11	16	12	10
Tuberculo-anaphylactic hypersensitive with 5 mg. tuberculo-protein as natural Seitz filtrate intravenously.....	0	10	12	20	15	13
Tuberculo-anaphylactic and desensitized with 5 mg. tuberculo-protein as natural Seitz filtrate intravenously and treated intravenously with natural Seitz filtrate...	0	11	11	18	13	10
Tuberculous (advanced disease).....	4	12	18	23	13	14
Tuberculous (slight disease).....	3	8	11	19	8	10

\* The tuberculin reaction is graded as usual from 0 to 4.

† The Seitz filtrate contained 1 mg. tuberculo-protein per cc.

‡ The autolytic tuberculin contained 10 per cent biologically active tuberculo-protein.

§ All heat-killed bacilli were removed from young cultures (10 to 14 days old) as free from tuberculin as possible.

desensitized or treated with Seitz filtrate (containing tuberculo-protein) or heat-killed tubercle bacilli. These findings are suggestive of the fact that an intoxica-

tion is being dealt with referable to the tuberculo-protein and tubercle bacilli rather than that there exists any specific immune phenomenon referable to the phagocytic cells. The phenomenon is not truly one of immunization or desensitization as usually termed but of specific intoxication accentuated by previous sensitizing contact with the intoxicating agent.

The method of eosin staining for cell death was essentially used by Schrek to determine the capacity of an agent to kill cells in suspension and appeared suitable to him for studying the toxicity of antiseptics. In view of the fact that tuberculin was found to retard or abolish phagocytosis of both staphylococci and tubercle bacilli when phagocytic cells were obtained from the blood of allergic hypersensitive or anaphylactic hypersensitive guinea pigs or the same type of animals treated with tuberculin, it seemed desirable to test by the Schrek technique of unstained cell counts whether the tuberculin also produced its toxic effects upon the phagocytic cells as determined by this method. The experiments were performed, therefore, using the bone marrow cells from the same sets of test animals that were utilized in the phagocytic experiments presented in tables 1 and 2 and with the same Seitz filtrate and autolytic tuberculin as test agents. The results of the cell death or unstained cell tests are recorded in table 3.

The findings recorded in table 3 indicate that no appreciable effect was discernible on the number of stained bone marrow cells as a result of various specific treatments, regardless whether the bone marrow cells were obtained from normal, allergic or anaphylactic hypersensitive guinea pigs or from the hypersensitive guinea pigs treated with tuberculin. It would appear, therefore, that while the toxicity produced by tuberculin upon phagocytosis by the phagocytic cells from tuberculo-tuberculin and bacillary hypersensitive guinea pigs was discernible, it did not reveal itself, within the limits of the tests used, when cell death was the criterion, as no appreciable change in the numbers of stained cells or the number of dead cells could be noted.

#### SUMMARY AND CONCLUSIONS

1. Tuberculin (tuberculo-protein) is relatively innocuous to the phagocytic cells from normal guinea pigs as measured by the phagocytosis of *Staphylococcus aureus* or human tubercle bacilli.

2. Tuberculin (tuberculo-protein) depresses the phagocytosis of the phagocytic blood cells of allergically tuberculin-hypersensitive, anaphylactically tuberculin-hypersensitive or tuberculous guinea pigs for staphylococci and human tubercle bacilli. This depression of phagocytosis of staphylococci and tubercle bacilli is accentuated markedly if the allergically tuberculin-hypersensitive or anaphylactically tuberculin-hypersensitive guinea pigs have been treated previously with tuberculin (tuberculo-protein) or heat-killed tubercle bacilli.

3. The depression of phagocytic activity of the phagocytic blood cells from allergically tuberculin-hypersensitive, anaphylactically tuberculin-hypersensitive or tuberculous guinea pigs, untreated or treated with tuberculin (tuberculo-protein), does not appear to be of the nature of a true immunization or desensiti-



zation but rather one of accentuated or cumulative tuberculin toxicity in the hypersensitive animals.

4. It is interesting to note that the phagocytic blood cells from specifically immune, allergically tuberculin-hypersensitive, anaphylactically hypersensitive or tuberculous guinea pigs phagocytize viable human tubercle bacilli equally well as the phagocytic blood cells obtained from normal guinea pigs.

5. The bone marrow cells from allergically tuberculin-hypersensitive, anaphylactically tuberculin-hypersensitive or tuberculous guinea pigs, whether from animals untreated or treated with tuberculin or heat-killed tubercle bacilli, revealed no appreciable difference as a result of contact with tuberculin (tuberculo-protein) when determined by the stained dead-cell technique.

#### SUMARIO Y CONCLUSIONES

1. Valorada por medio de la fagocitosis del *Staphylococcus aureus* o de los bacilos tuberculosos humanos, la tuberculina (tuberculoproteína) es relativamente inocua para los fagocitos de los cobayos normales.

2. La tuberculina (tuberculoproteína) deprime la fagocitosis de los cobayos alérgica o anafilácticamente tuberculino-hipersensibles o tuberculosos, para los estafilococos y los bacilos tuberculosos humanos. Esta depresión acentúase decididamente si los cobayos alérgica o anafilácticamente tuberculino-hipersensibles han sido tratados previamente con tuberculina (tuberculoproteína) o con bacilos tuberculosos muertos al calor.

3. La hipofagocitosis de los cobayos alérgica o anafilácticamente tuberculino-hipersensibles o tuberculosos, ya tratados o no con tuberculina (tuberculoproteína), no parece participar de la naturaleza de una verdadera inmunización o desensibilización sino más bien de una toxicidad acentuada o acumulativa a la tuberculina en los animales hipersensibles.

4. Es interesante observar que los fagocitos procedentes de cobayos específicamente inmunes, alérgica o anafilácticamente tuberculino-hipersensibles o tuberculosos, fagocitan los bacilos tuberculosos humanos viables igualmente bien que los fagocitos obtenidos de cobayos normales.

5. Las células de la médula ósea procedentes de cobayos alérgica o anafilácticamente tuberculino-hipersensibles o tuberculosos, ya hayan sido éstos tratados o no con tuberculina o con bacilos tuberculosos muertos al calor, no revelaron mayor diferencia debido al contacto con la tuberculina (tuberculoproteína) cuando se usó para la determinación la técnica de las células muertas teñidas.

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# SPLEEN-APPEARANCE TIME OF TUBERCLE BACILLI<sup>1,2</sup>

## As Related to Dosage of Bacilli

C. E. WOODRUFF, RUBY G. KELLY AND MARY A. LEAMING

Rapid and wide-spread dissemination of tubercle bacilli from their point of introduction to the body has been established by numerous workers. Krause and Willis (1), for example, demonstrated that tubercle bacilli have spread beyond the field of infection within three hours after inoculation and have made the circuit of the animal body within three to four days. Boquet and Laporte (2) found that tubercle bacilli of the human type inoculated in the groin of normal guinea pigs have reached the spleen in fifteen days, while Corper and Cohn (3) recovered tubercle bacilli from the spleen twenty-four hours after inoculating the animals with large doses of tubercle bacilli suspended in oil.

The well established facts concerning the dissemination of tubercle bacilli suggested utilization of this characteristic as a test of virulence of the micro-organism. Trying out such a hypothesis involved first determining definitely, for a single strain of tubercle bacilli, the effect of dosage on the time required for the bacilli to reach the spleen following subcutaneous inoculation. This has been done. The work included 57 experimental series and involved culturing the spleens of 846 guinea pigs, sacrificed at daily intervals following their subcutaneous inoculation with the required dose of tubercle bacilli.

### METHOD

The Gary strain of human type *M. tuberculosis* was used throughout the experiments. This strain, isolated from a 73-year-old woman with chronic, cavitary tuberculosis, has been subcultured for the past eighteen years without appreciable change in virulence. All of the bacilli employed in making the inocula were grown on Loewenstein's medium. In each case a small amount of a one to three weeks old culture was weighed on a chemical balance. The bacilli were then carefully triturated, using a sterile mortar and pestle, and sterile saline was added drop by drop until a creamy suspension had been obtained. After this the saline was added more rapidly until the desired weight of tubercle bacilli was contained in 0.5 cc. of saline. Also a weighed amount of finely ground sterile charcoal was added to the inoculum so that the site of inoculation in the guinea pig could be identified. In every case the volume of inoculum used for each animal was the same—0.5 cc.—and contained 0.01 mg. of charcoal<sup>3</sup> plus the desired weight of tubercle bacilli. The latter varied from 1 mg. to  $10^{-6}$  mg.

<sup>1</sup> From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

<sup>2</sup> Aided by a grant from the Committee on Medical Research of the National Tuberculosis Association.

<sup>3</sup> Our experience has been similar to Corper's (4) in determining that the inclusion of minute amounts of finely divided carbon with the inoculum has no effect on the development of tuberculosis in the animal.

The heavier suspensions always contained clumps of tubercle bacilli, no attempt being made to remove them.

Most of the guinea pigs used in the experiments were small, varying in weight from 150 to 300 g. They were inoculated subcutaneously in the right axilla, great care being employed to make the dose for each pig in a given series as uniform as possible. Before each inoculation the suspension of tubercle bacilli was stirred, and only 0.5 cc. at a time was taken into the syringe—this to avoid the rapid sedimentation which may cause gross variations in dosage if more inoculum is drawn into the syringe at one time. The axillary region was utilized since inoculations in that area can be made rapidly with the assurance that the inoculum will be deposited in the subcutaneous tissue. There is no danger of accidentally entering the peritoneal cavity as may happen when inoculations are made in the groin.

From animals sacrificed at daily intervals the spleen<sup>4</sup> was removed with aseptic precautions. The amount of spleen used for culturing depended upon the size of the organ. If the spleen weighed 0.5 g. or less the entire organ was used. In the case of spleens weighing more than 0.5 g. only half the organ was employed. The splenic tissue was triturated in a sterile mortar, sterile saline being added slowly until a total volume of 5 cc. of splenic suspension had been achieved. One-tenth of the entire suspension (0.5 cc.) was then inoculated directly on 6 tubes of Loewenstein's medium. At the same time another 6 tubes of medium were inoculated with 0.5 cc. of the suspension which had been treated with hydrochloric acid and sodium hydroxide to kill any contaminating pyogenic microorganisms. Thus one-tenth or one-twentieth of the spleen, depending upon whether the whole or only half of the spleen was triturated, was inoculated both directly and after the decontaminating treatment. If tubercles were grossly visible in the spleen, seeding of media was also made at higher dilutions such as one-hundredth and one-thousandth.

The cultures of splenic tissue were examined at biweekly intervals over a period of two months to determine whether a given spleen did or did not contain tubercle bacilli. At each examination the number of colonies of tubercle bacilli which appeared on the tubes was counted. From the total colony count, knowing the proper dilution factor, it was possible to estimate the number of tubercle bacilli in each spleen.

#### RESULTS

Data for the study are summarized in table 1, the results for each dose at a given time interval being expressed as a ratio. Thus the first ratio encountered, 15/5, indicates that 20 guinea pigs were sacrificed on the first day after their subcutaneous inoculation with 1 mg. of tubercle bacilli. Of these 20 pigs, 15 had spleens which proved to be "positive" for tubercle bacilli, while in 5 instances the spleen cultures were negative. After the first day the spleens of animals receiving this dose were invariably positive.

<sup>4</sup> The spleen is the organ of choice for demonstrating blood-stream dissemination since, as Krause (5) has said, "In guinea pigs . . . the spleen is undoubtedly the organ that is most prone to tubercle."

In animals inoculated with 0.1 mg. of tubercle bacilli only one of the 7 guinea pigs sacrificed at twenty-four hours showed a positive spleen culture. On the second day, however, 9 out of 13 animals yielded a positive culture. When 0.01 mg. of bacilli was used as the inoculum it was not until the fourth day after inoculation that the majority of the spleens was found to contain tubercle bacilli; and so on through the table, the elapsed time before appearance of positive cultures becoming progressively greater the smaller the dose of tubercle bacilli. This time interval which elapses before one may *expect* to recover tubercle bacilli from the spleen of a guinea pig following a given dose of tubercle bacilli, has been

TABLE 1  
*Spleen-appearance time of tubercle bacilli as related to dosage*

TIME AFTER INOCULATION	AMOUNT OF INOCULUM (SUBCUTANEOUS)						
	1 mg.	$10^{-1}$ mg.	$10^{-2}$ mg.	$10^{-3}$ mg.	$10^{-4}$ mg.	$10^{-5}$ mg.	$10^{-6}$ mg.
	Spleens positive or negative for tubercle bacilli						
<i>in days</i>							
1	15/5*	1/6	0/14	0/4	0/3	0/3	0/1
2	9/0	9/4	5/16	0/3	0/3	0/3	0/2
3	4/0	11/2	8/11	0/6	0/3	0/4	0/1
4	3/0	6/0	13/6	1/7	0/4	0/3	0/2
5	4/0	3/0	10/3	1/7	0/2	0/4	0/1
6	3/0	7/0	5/0	3/7	1/7	0/4	0/2
7	4/0	6/0	7/0	5/12	1/6	0/6	0/4
8	3/0	4/0	6/0	6/2	1/8	0/4	0/2
9	4/0	3/0	10/0	7/2	5/3	1/6	0/2
10	1/0	4/0	6/0	3/0	8/2	2/7	1/9
11	2/0	2/0	7/0	3/0	8/1	6/4	1/9
12	3/0	6/0	7/0	4/0	8/2	8/3	8/4
13	2/0	2/0	4/0	2/0	6/1	7/1	7/2
14	1/0	3/0	7/0	2/0	5/0	9/0	6/1
15	5/0	5/0	9/0	5/0	4/0	5/0	5/1
16	1/0	4/0	7/0	2/0	2/0	1/0	3/0
17	2/0	4/0	5/0	4/0	1/0	1/0	3/0
18	1/0	2/0	2/0	4/0	3/0	2/0	3/1
19-42	5/0	26/0	19/0	34/0	11/0	15/0	9/0

\* Pos./Neg.

termed *spleen-appearance time*. From table 1 it will be seen that this interval, under the conditions of the experiment, varies inversely with dosage as follows: 1 mg., one day; 0.1 mg., two days; 0.01 mg., four days; 0.001 mg., eight days;  $10^{-4}$  mg., nine days;  $10^{-5}$  mg., eleven days;  $10^{-6}$  mg., twelve days.

#### NUMBER OF TUBERCLE BACILLI IN THE SPLEEN

Table 2 shows, for one of the experimental series, the number of tubercle bacilli found in each spleen, as indicated by the colony count. A difference will be noted in the manner of appearance of tubercle bacilli in the four groups of

animals. Guinea pigs inoculated with 1 mg. of tubercle bacilli usually show bacilli in the spleen on the first day, following which there is a gradual increase in the count of bacilli over a period of several days. In the animals inoculated with the smaller doses, on the other hand, the tubercle bacilli appear in the spleen more abruptly and show a more rapid increase in numbers.

## INFLAMMATION, ALLERGY AND SPLEEN-APPEARANCE TIME

Histological changes at the site of inoculation were studied in each animal. The specific area involved was readily identified because of the charcoal which had been included in the inoculum (figure 1). In each animal the charcoal-containing tissue was removed and divided in half, the two parts being teased out on glass slides. One tissue preparation was stained by Wright's method and the other by the Ziehl-Neelsen technique. It was found that in animals

TABLE 2  
*Effect of time and dosage on number of bacilli in spleen*  
(5740 series)

TIME	DOSE OF TUBERCLE BACILLI			
	1 mg.	$10^{-2}$ mg.	$10^{-4}$ mg.	$10^{-6}$ mg.
	Number of Bacilli in Spleen			
<i>in days</i>				
1	10			
2	40	0		0
4	160	0	0	0
6	540	160	0	0
8	1,860	940	0	0
11	212,000	2,000	560	0
12		14,000	480	20
13		6,000	4,400	860
15	3,600,000	120,000	24,000	1,560
20		4,000,000	320,000	24,000

inoculated with 1 mg. of tubercle bacilli an inflammatory reaction, with the appearance of polymorphonuclear leucocytes, was present within an hour after inoculation. By the end of twenty-four hours inflammation was grossly visible.

The inflammatory response is progressively slower in animals inoculated with the smaller doses. Four days after the inoculation of 0.001 mg. of tubercle bacilli, for example, microscopic examination of the local lesion reveals large numbers of tubercle bacilli growing without any interference from inflammatory cells (figure 2). On the tenth day a small nodule will be found at the site of inoculation of the 0.001 mg. dose and a smear will show that polymorphonuclear leucocytes have begun to phagocytose the tubercle bacilli (figure 3). Ten days after the inoculation of  $10^{-5}$  mg. of bacilli, on the other hand, microscopic examination of the lesion usually will still reveal the free and unencumbered growth of tubercle bacilli (figure 4). This sequence of events, noted throughout our

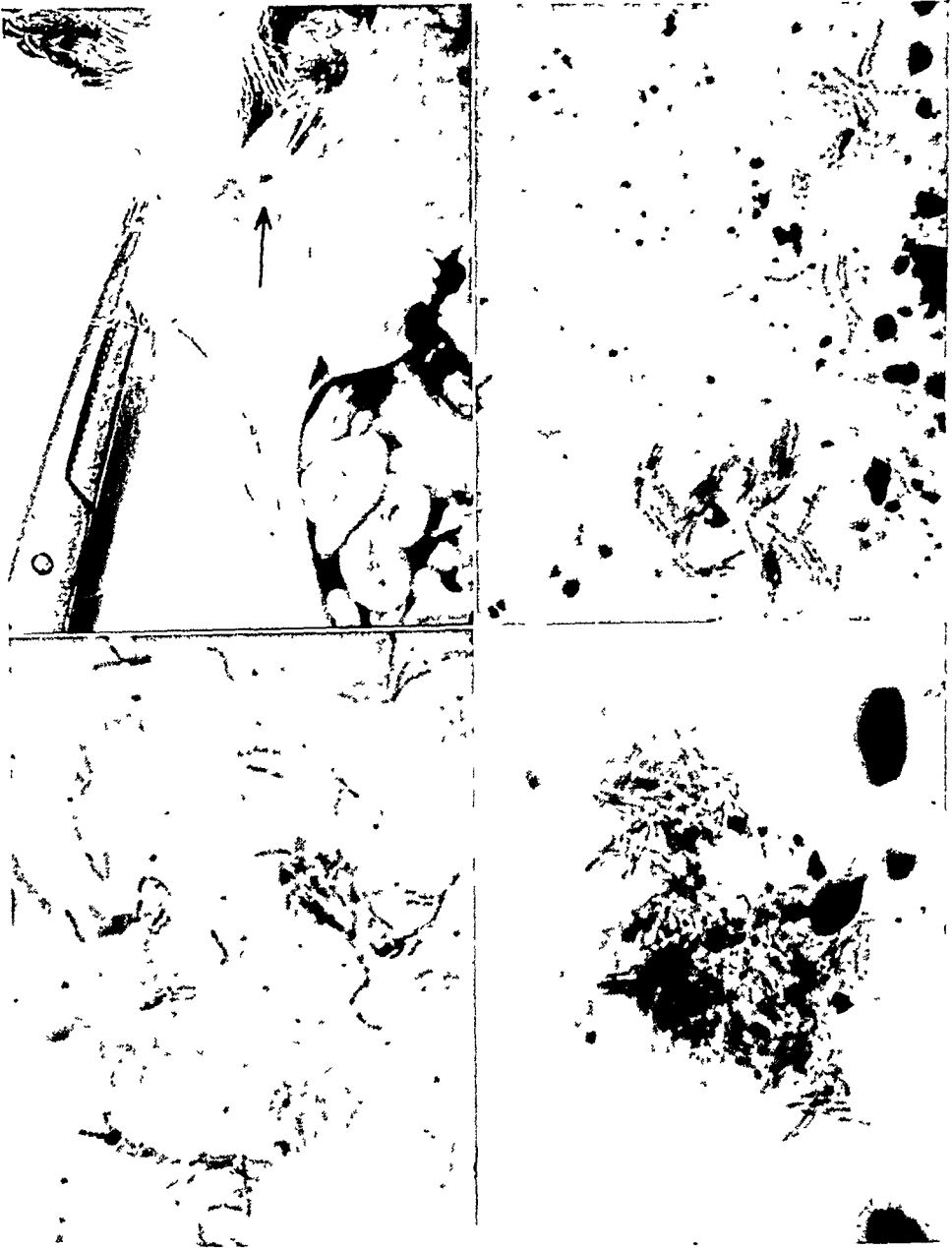


FIG 1 (Upper left). Arrow points to site of inoculation of tubercle bacilli in guinea pig axilla marked by charcoal included in the inoculum.  $\times 1$

FIG. 2 (Upper right). Freely growing bacilli in axilla of guinea pig four days after the inoculation of 0.001 mg of tubercle bacilli. The black particles are bits of charcoal.  $\times 1500$

FIG 3 (Lower left) Inflammatory cells and tubercle bacilli in axilla of guinea pig ten days after the inoculation of 0.001 mg. of tubercle bacilli.  $\times 1500$

FIG 4 (Lower right) Freely growing bacilli in axilla of guinea pig ten days after the inoculation of  $10^{-5}$  mg of tubercle bacilli. The black particles are bits of charcoal.  $\times 1500$

various experimental series, indicates that during the first few days after the inoculation of minute doses of tubercle bacilli there ensues a free growth period (6, 7) during which the bacilli proliferate in perfect symbiosis with the cells of the

animal body. The length of this period bears an inverse ratio to the number of tubercle bacilli in the inoculum. Following the 1 mg. dose there is no free growth period at all since, as noted above, polymorphonuclear leucocytes begin phagocytosing the inoculated bacilli within an hour. At the other extreme, the free growth period continues for ten or eleven days after the inoculation of  $10^{-6}$  mg. of bacilli.

The appearance of tubercle bacilli in the spleen is definitely related to the initiation of inflammation at the site of inoculation—or, conversely, to the termination of the free growth period. Invariably it was noted that inflammation, with the appearance of polymorphonuclear leucocytes at the site of inoculation, preceded the obtaining of a positive spleen culture. In other words, the free growth period had always come to an end before tubercle bacilli could be found in the spleen. This is what one might expect, assuming that phagocytosis of tubercle bacilli by leucocytes is necessary before the bacteria can gain access to the blood-stream (8).

About one-third of the total number of 846 guinea pigs was tested with 1 mg. of OT given intracutaneously at or near the spleen-appearance time. If tubercle bacilli had not yet reached the spleen, the skin test was invariably negative. On the other hand, in every animal with a positive skin test tubercle bacilli could be demonstrated in the spleen. These facts indicate that in guinea pigs inoculated subcutaneously with living tubercle bacilli the bacilli reach the spleen before the development of allergy in the animal.

#### SPLEEN-APPEARANCE TIME AS A TEST FOR VIRULENCE

As might be expected, nonpathogenic acid-fast bacilli react in a characteristic way when tested for spleen-appearance time. *M. phlei*, for example, when inoculated in a dose of 1 mg., reaches the spleen after only five hours—sooner than tubercle bacilli. However, *M. phlei* does not multiply in the spleen and disappears from that organ by the end of a week. After the injection of small doses, such as  $10^{-4}$  mg., *M. phlei* does not reach the spleen at all. The butter bacillus, *M. butyricum*, reacts to the test in a manner similar to *M. phlei*. The well known strain R<sub>1</sub> reaches the spleen inconsistently and only after considerable delay. A strain of BCG, tested in doses of 0.01 mg., failed to reach the spleen at all.

However, the hope was that spleen-appearance time might show minor variations between strains of tubercle bacilli supposedly fully virulent. In preliminary studies the H37RV<sup>5</sup> strain and a recently isolated strain called Brownlee have been tested against the Gary strain. The results of these studies fail to reveal any significant difference in spleen-appearance time between the three strains.

#### DISCUSSION

It has been taught (9) that in the normal animal the first response to infection with tubercle bacilli is proliferative in nature; that acute inflammation with an outpouring of polymorphonuclear leucocytes occurs only after allergy has been

<sup>5</sup> This strain of tubercle bacilli was kindly furnished by Wm. Steenken, Jr.



established. The same opinion was expressed in a previous communication from this laboratory (7) when the ending of the free growth period of tubercle bacilli by an influx of polymorphonuclear leucocytes was ascribed to the development of allergy in the animal. The more careful examination of time relationships which was possible in the present study makes it evident that this is not true. For example, inflammatory cells appear at the point of inoculation of 1 mg. of tubercle bacilli after only one hour, which is four or five days before the first signs of allergy can be demonstrated. When smaller doses of tubercle bacilli are employed, the bacilli may proliferate in symbiosis with the tissue cells for a considerable period of time. Eventually, however, polymorphonuclear leucocytes appear *before* the development of allergy in the animal. It is probable that, after inoculation of the smaller doses, uninterrupted proliferation of the tubercle bacilli continues until the local tissues are damaged mechanically by the accumulation of bacilli. Often the freely growing bacilli are found in such masses (figure 4) that growth and respiration on the part of the tissue cells would seem impossible. Direct cell injury of this type is probably responsible for the initial outpouring of polymorphonuclear leucocytes.

The failure in some of the older experimental work (10) to notice the initial polymorphonuclear reaction in primary tuberculous infection may be ascribed to inadequate marking of the site of inoculation. It is only by some means such as the inclusion of carbon in the inoculum that the area where a few tubercle bacilli are proliferating can be identified during the earliest stages of development of the lesion.

The fact that three strains of tubercle bacilli of such diverse origins as H37RV, Brownlee and Gary have spleen-appearance times which appear to be similar, within the limits of experimental error, makes one skeptical concerning the possibility of distinguishing minor variations in the virulence of tubercle bacilli by this method. More promising is the use of spleen-appearance time as a screening test in determining what drugs may have therapeutic effects in experimental tuberculosis. A preliminary study, using the spleen-appearance test, has been made with animals treated with diasone. This study, to be detailed in a subsequent publication, indicates a significant variation in spleen-appearance time in the treated animals.

Certain precautions should be mentioned with regard to making use of spleen-appearance time in experimental studies. Cultures to be compared should be of the same age. They should be young and of vigorous growth. All inoculations should be made at one site and with care to secure uniformity of dosage. Table 1 is worked out for animals inoculated in the axilla. If a more peripheral inoculating site such as the groin should be used one might expect an increase in the spleen-appearance time. Because of the longer spleen-appearance interval a dose of  $10^{-4}$  or  $10^{-5}$  mg. has been found preferable to larger doses in comparative tests. Finally, to allow for possible variations in the response of individual guinea pigs, one should be prepared to sacrifice at least 5 pigs on the expected day of spleen-appearance and 3 to 4 animals on the preceding and the following day.

## SUMMARY

The time required for tubercle bacilli to reach the spleen of a guinea pig following subcutaneous inoculation (spleen-appearance time) has been established for one strain of tubercle bacilli.

Inflammation at the site of inoculation and the appearance of tubercle bacilli in the spleen precede the development of allergy in the experimental animal.

## SUMARIO

En lo tocante a una cepa, se ha establecido el tiempo que necesitan los bacilos tuberculosos para llegar al bazo de un cobayo después de la inoculación subcutánea (tiempo de aparición esplénica).

La inflamación en el sitio de la inoculación y la aparición de bacilos tuberculosos en el bazo preceden la producción de alergia en el animal de experimentación.

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## CHEMOTHERAPEUTIC TESTING IN EXPERIMENTAL TUBERCULOSIS

### Suggested Outline of Laboratory Procedures for Testing Antituberculosis Substances in Experimentally Infected Animals

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As more investigators enter the field of chemotherapy of tuberculosis, it would seem desirable that a more or less standardized procedure be followed in testing the value of new compounds. The following suggestions are formulated from our experiences of the past five years. The procedures described have proved relatively simple and reliable in that promising drugs have by repeated experimentation given favorable results in experimental tuberculosis of guinea pigs, while those that were considered noneffective have on restudy failed to be effective.

Before proceeding with an outline of the methods we suggest for testing the therapeutic efficacy of a compound, we should set forth what we consider to be the critical requirements for a satisfactory chemotherapeutic agent for combating infections experimentally induced in animals. These are briefly as follows:

(1) The agent should be well tolerated and not produce serious or irreversible physiological derangements.

(2) The substance should reverse a well established inoculation tuberculosis, induced by a strain of human tubercle bacilli of standard virulence, from a progressive, destructive process to one that is nonprogressive and will eventually resolve, fibrose or calcify. The obvious consequence of such effects would be the extended longevity of the treated animals.

(3) The substance should eliminate or render avirulent tubercle bacilli from the organs of predilection, such as the spleen, lungs and liver, and hence preclude subsequent activity of possible latent infections.

(4) The desired results should be obtained within a reasonable period of treatment. In estimating what this time interval should be, one must recall that the lesions of tuberculosis are slow to heal. Experience suggests that in guinea pigs six months is a reasonable period for such healing.

### SUGGESTED PROCEDURES

Since up to now we are unaware of any *in vitro* procedure in which the results can be consistently correlated with results by *in vivo* methods, we do not subscribe to *in vitro* procedures as means of distinguishing substances that may prove effective *in vivo*. We would, however, recognize the great value of a reliable *in vitro* test should one be developed and we strongly urge that search for such a method be continued. However, it is our opinion that until *in vitro* methods are found which are capable of yielding results which correlate adequately with

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animal experiments, it appears clear that the *in vitro* approach is fruitless even as a screening procedure.

*Animals:* At the present time the guinea pig is the animal of choice. Cage mates should be of the same sex, preferably males. Young vigorous animals weighing 400 to 500 g. each are preferred. If guinea pigs are purchased from dealers or are obtained from local breeders they should be tuberculin-tested before being accepted for experiments. The animals should be selected with care so as to eliminate those whose physical state is below normal. The possibility of using successfully species of animals other than the guinea pig is recognized. However, the universality of the use of guinea pigs in research on tuberculosis has established this animal as being a dependable and highly susceptible host for human tubercle bacilli. When it is infected with virulent organisms the results are predictable, thus providing a reliable base-line by which the effects of deterrent agents may be judged with confidence.

*Feed and care of animals:* Probably the most important single factor in a successful *in vivo* experiment is an intelligent and conscientious animal attendant. The animals should be housed in a room free from drafts and an even temperature should be maintained. (The temperature should be 70 to 75°F.) The feed chosen should be that likely to be available for the duration of the experiment. Commercially prepared rabbit chow is satisfactory, provided the prepared feed is supplemented three times weekly with uncooked cabbage or other fresh vegetables. (Unlike rabbits, guinea pigs do not synthesize vitamin C.) We have also included corn syrup as an adhesive agent for insoluble drugs. Corn syrup serves as a flavoring agent and as an additional source of calories. The control or untreated animals also receive corn syrup as part of their diet.<sup>3</sup> Fresh water should be supplied daily in each cage. The necessity for sanitation is obvious.

Guinea pigs to be used in an experiment should be selected a week or so in advance so that they may become familiar with their surroundings and accustomed to their diet.

*Infective inoculum:* The virulent variant of Saranac strain H37 is recommended. The history of this organism is well known and subcultures can be obtained from the Trudeau Research Laboratory, Saranac Lake, New York, upon request. It is very important that this strain be cultured continuously in the synthetic medium proposed by Proskauer and Beck.<sup>4</sup> Subcultures should be made regularly every two to three weeks.

For experiments of short duration when rapidly progressive disease is required the dose of tubercle bacilli for guinea pigs should be 0.1 mg. inoculated subcutaneously. For long-term experiments requiring slowly progressive but invariably fatal disease we recommend a dose 0.001 to 0.0005 mg. inoculated subcutaneously. Care should be taken to insure a fine and uniform suspension of the bacteria constituting the inoculum. The suspension should be prepared just prior to use.

*Test substances:* Certain information of a pharmacological character should be

<sup>3</sup> See addenda for procedure of mixing substances to be tested with feed.

<sup>4</sup> The preparation of this medium is described in the addenda.

available before any new drug or other substance is used in an *in vivo* experiment in chemotherapy. Information on the following points is necessary: (1) optimal dose (this is the amount that may be given continuously without causing the animal to lose weight or evince other signs of toxicity); (2) concentration of the substance in the blood after peroral and, if the substance is soluble, after parenteral administration; (3) dose schedule necessary to maintain satisfactory blood concentration and (4) complete available information regarding the chemistry of the substance to be studied. The usual data relating to acute toxicity experiments have not been particularly useful in our experience.

*Administration of test substance:* If satisfactory blood concentration can be obtained following peroral administration the substances being tested may be given by stomach tube or mixed with the feed. The latter method of administration is preferred, since it is more physiological and less laborious than the others and insures a gradual but more or less continuous intake of the medicament during each twenty-four hours.

We recognize the theoretical advantages of administration of accurately weighed quantities of the drug by stomach tube but the practical advantages of administration with the feed predominate in our opinion for experiments which are not designed to be quantitative. Reasonably accurate records of drug intake may be obtained by weighing the amount of food consumed each day. The intubation of guinea pigs involves much additional handling of animals and may interfere with their nutrition. It also exposes laboratory personnel to real dangers of contracting tuberculosis.

It may be desirable to test substances that are not absorbed by the digestive tract or which may actually be destroyed or rendered inert when given by mouth and yet might be highly effective when given parenterally. Likewise substances that may be effective when given perorally may not necessarily be effective when administered by other routes. Obviously the route of administration must depend upon the character of the particular substance under consideration.

*Preliminary or screening test (prophylactic chemotherapy):* A minimum of 6 to 10 guinea pigs should be allocated for each agent to be tested and a similar number of animals used for controls. For the purpose of comparison of relative efficacy it is important also to include a group of animals to which is given an agent of known effectiveness. We have used either promin<sup>5</sup> or 4,4'-diaminodiphenylsulfone for this purpose. Administration of the drugs should be started two to four days prior to inoculation with tubercle bacilli. All animals are then inoculated subcutaneously with 0.1 mg. of the infective bacteria. The drug should be administered daily and the experiment continued for sixty days after infection.

Immediately preceding necropsy, specimens of blood should be removed by cardiac puncture for determination of blood concentrations. Also material for other hematological studies should be obtained. These studies include: (1) determination of hemoglobin, (2) total number of erythrocytes, (3) total number of leucocytes and (4) number of reticulocytes. From each animal tissues representing the spleen, liver, both lungs, the tracheobronchial lymph nodes and at least

<sup>5</sup> Sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate.

one kidney should be preserved in a suitable fixative solution for the preparation of histological sections.

Since very few of the animals of the control group are likely to have died during the sixty-day period of infection, evidence of the effects of the test substance must be obtained from the relative amounts and character of tuberculosis present in the organs of predilection, such as the spleen, lungs and liver.

The impressions gained from the gross examination of the tissues are subsequently verified by histological study of the tissues.<sup>6</sup> Experience has clearly shown that histological examination reveals a great deal of valuable information, including revelation of otherwise undetected tuberculosis and a clearer view of reactive effects. Proof of infection in treated animals is often obtained by demonstration of otherwise invisible healing foci.

*Crucial test:* Substances that exert desirable or favorable effects on the expected development of the disease in the preliminary test must be subjected to an experiment of more rigorous conditions. The important and essential feature of such an experiment is the presence in the animals to be treated of a tuberculous infection established six weeks before therapy is started.

Groups of at least 20 animals each are provided for each substance to be subjected to a crucial experiment and a like number for the control or untreated group. In addition, a group of 20 animals should be treated with a compound of known effectiveness.

All animals are inoculated subcutaneously with tubercle bacilli in doses of 0.001 mg. or 0.0005 mg. Forty days later the intracutaneous tuberculin test is applied (OT in 1:100 dilution). Animals in which the test fails to elicit a definitely positive reaction are not acceptable for subsequent therapy.

The administration of the therapeutic substance is started on the forty-second day after infection. The experiment is continued (1) until all of the untreated animals have died or (2) until the animals have received treatment for a period of six months. Before the experiment is brought to a close it may be of interest to test all of the survivors again with tuberculin.

Tissues from the site of inoculation, the regional lymph nodes, the spleen, liver, lungs and tracheobronchial lymph nodes of all of the animals should be preserved for the making of sections for histological study. From the animals killed when the experiment is terminated specimens of blood should be obtained for the same determinations required from animals in the preliminary or screening test.

The spleens of animals in treated groups in which there are no signs of tuberculosis in the spleen, liver or lungs, are removed aseptically. One-half of each spleen is ground and suspended in sterile physiological solution of sodium chloride for inoculation into 2 normal guinea pigs. This is for the purpose of detecting the presence of virulent tubercle bacilli that may be present in the tissues of treated animals, even though recognizable tissue changes are not present. The guinea pigs inoculated with the splenic suspensions are killed eight weeks after inoculation and examined for tuberculosis.

<sup>6</sup> A scheme for recording tuberculous changes numerically has been described previously (1).

## Key of Symbols

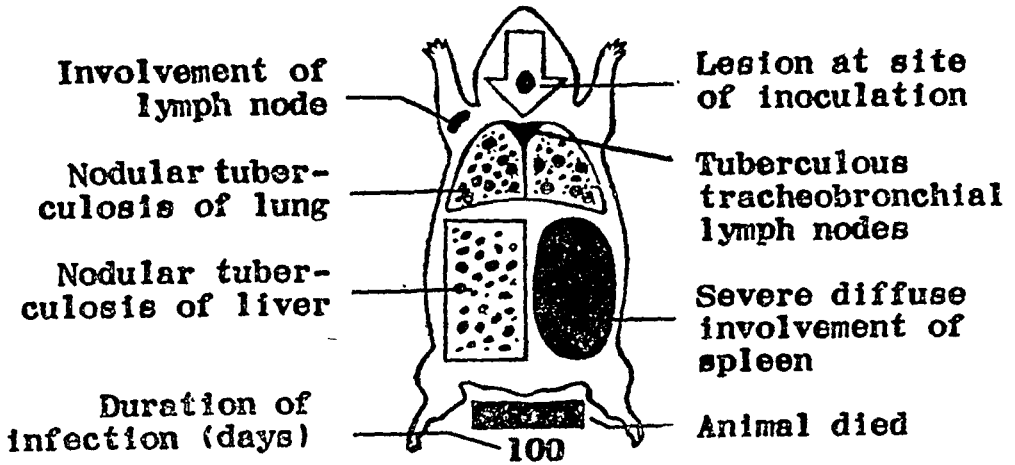


FIG. 1. Schematic representation showing tuberculous lesions in sites of predilection of an experimentally infected guinea pig.

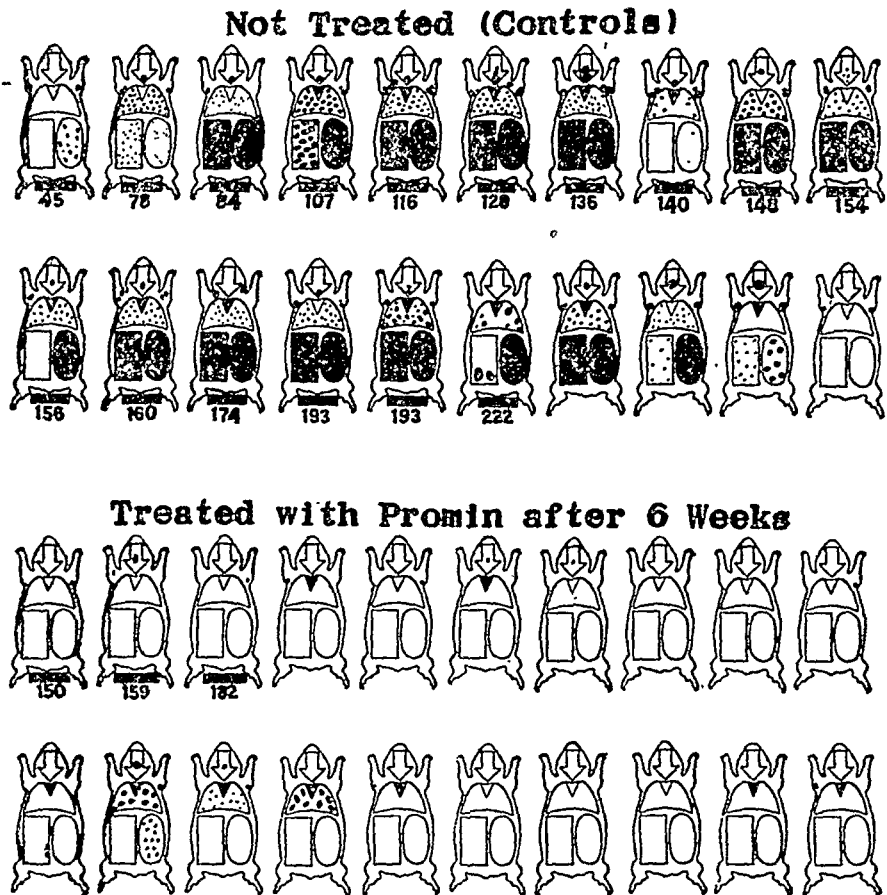


FIG. 2. Results of typical experiment showing amounts and situations of tuberculous changes in two groups of guinea pigs consisting of 20 animals each. The marked differences in the amount of disease in the respective groups is apparent at a glance. The distinctive short black line under many of the schematic outlines indicates that these particular animals died. The numerals represent the days of life after inoculation.

Conclusions regarding the effectiveness of the substances tested are dependent on the following: (1) relative survival times of the treated and untreated groups of animals; (2) the amount and the character of the tuberculous lesions in the respective groups determined by histopathological studies; (3) evidence of toxicity as revealed by the studies of the blood, kidneys, liver and so forth; and (4) the presence or absence of virulent tubercle bacilli in tissues apparently without signs of active lesions.

*Recording of results:* An accurate, simple and convenient method of recording lesions of experimentally induced tuberculosis of guinea pigs has been developed and used in this laboratory during the past five years and has proved to be a convenient aid.

A schematic representation of the various organs of a guinea pig (figure 1) is printed upon the record card of each animal by means of a large rubber stamp measuring approximately 2 by 4 inches. At the time of necropsy an observer records the lesions, noted grossly, by sketching the approximate size and form of these lesions with a red pencil. If the disease is too extensive for lesions to be recorded individually the whole organ is colored red. Appropriate marginal notes can be made at this time to indicate size and appearance of organs.

These cards demonstrate, with minimal effort, the gross pathological appearances in a much clearer manner than could possibly be achieved by any verbal descriptions, regardless of how carefully or extensively these might be written. When such cards are arranged for display the comparative effectiveness of various compounds becomes clearly evident (figure 2).

#### COMMENT

A chemotherapeutic substance to be considered really effective must yield results that are unequivocal. Although an ideal substance would be one that satisfies all of the critical requirements set forth previously, failure of a substance to meet all of these exacting demands does not necessarily imply that its use in clinical tuberculosis is contraindicated. However, it cannot be stated too emphatically that no substance should be tried therapeutically on human beings until its effectiveness and relative safety have been definitely established by properly conducted and adequate animal experiments.

An additional and important advantage of the *in vivo* procedure over the *in vitro* method of testing tuberculotherapeutic substances is the opportunity to detect gross and microscopic tissue changes indicative of toxic effects. Substances that might prove highly effective under *in vitro* conditions may be so toxic as to be unsuitable for animal experimentation. While it is recognized that severe toxic effects may be exerted *in vivo* without inducing demonstrable anatomical changes, the necessity for examining the parenchymal tissues for possible morphological alterations, especially in animals treated with substances that might be used clinically, is obvious. It is true that this information can be obtained by separate pharmacological studies but much time can be saved by obtaining from the same experiment (1) data concerning the ability of the therapeutic substance to combat the tubercle bacillus and (2) pharmacological evidence as to the relative safety of the substance after administration for a prolonged



period. Since very little is usually known about the toxic properties of compounds tested for their possible tuberculotherapeutic effects, the microscopic examination of tissues becomes an important part of the study of any substances having promising possibilities.

The contrasts between tuberculosis of the experimental animal and that of the human being are unavoidably great and every effort should be made to lessen these contrasts. There is considerable need for an animal in which tuberculous disease comparable to tuberculosis in human beings is capable of developing. Possibly the dog would qualify best in this regard but the size of this animal and the difficulty of establishing uniform disease appear to preclude the dog from any consideration as an animal for screening tests of chemotherapeutic compounds.

As is well known, the pathological characteristics of experimental tuberculosis are greatly dependent upon (1) the number of tubercle bacilli injected, (2) the virulence of the organisms and (3) the route of inoculation. If an insufficient number of bacilli be administered or if the bacilli be of inadequate virulence, the results may be inconclusive because in some of the controls the disease fails to develop in a lethal form. If the inoculum be too big or if the animals be inoculated intravenously, the pathological changes wrought in the tissues are accelerated and are quite dissimilar to human tuberculosis and to the more mature forms of the disease in animals.

At the present time we have formed the tentative opinion that the handicap imposed by delaying treatment of the guinea pig for six weeks or longer, after a small inoculum of virulent tubercle bacilli has been introduced subcutaneously, yields a truer measure of therapeutic efficacy than could be obtained by massive infection and immediate treatment. In other words, therapy of advanced, pathologically mature tuberculosis should be more significant than prophylaxis of tuberculous bacillemia. The pathologist would regard these as separate disease entities even though the causative organism be identical in the two instances. Tuberculosis, as it occurs naturally, is ordinarily a chronic granulomatous disease and treatment cannot usually be provided at an early stage of infection. Such a disease is quite unlike the acute infectious diseases which have been studied so extensively by the experimental chemotherapist.

Investigators may be eager to place a great handicap upon a drug used experimentally by utilizing it in fulminating experimental tuberculosis only. It could be reasoned that a chemical remedy effective against an overwhelming inoculum administered intraperitoneally or intravenously should be even more effective against more chronic types of tuberculosis. Such correlation remains to be demonstrated and serious objections appear to these conclusions when the pathologist notes that tuberculosis produced in experimental animals is so different when the route of administration and number of bacilli are varied. The tuberculous bacillemia produced by an overwhelming inoculum may kill the animal before the allergic factors have come into play and before the familiar pattern of tissue changes characteristic of clinical tuberculosis has appeared. Should investigators wish to study chemotherapy of such experimental tuberculosis, we

would suggest that parallel experiments of long duration be simultaneously performed.

At this time the most important obstacle to a more rapid advance in chemotherapy of tuberculosis is the absence of a reliable means whereby effective substances can be definitely distinguished from the noneffective ones by procedures of short duration. This problem is now being investigated and it is possible that eventually a dependable *in vitro* method will be evolved. Furthermore, the *in vivo* approach to a more rapid method is not without promise. However, until either *in vitro* or *in vivo* methods of short duration have demonstrated their ability to provide results that can be correlated with the results of longer term *in vivo* procedures, the latter must remain the methods of choice.

#### ADDENDA

##### *Procedure for Incorporating in the Feed Substances Intended for Chemotherapy of Experimental Tuberculosis in Guinea Pigs*

- I. To prepare the meal form of rabbit chow (not pellets):
  - A. Weigh out 1,500 g. of the rabbit chow.
  - B. If the drug is insoluble in water, add the required amount of drug direct in dry form to the feed and mix thoroughly with the hands. Then add to the mixture a well mixed solution containing 100 cc. of warm water and 50 cc. of corn syrup (Karo Blue Label). Mix thoroughly.
  - C. If the drug is soluble in water, the requisite amount of drug is dissolved in 100 cc. of warm water. To this add 50 cc. of corn syrup, mix well and pour the mixture over the dry feed. Mix thoroughly with the hands.
- II. To prepare rabbit chow, pellet form:
  - A. Weigh out 1,500 g. of pellets.
  - B. If the drug is insoluble, add the drug in the dry form to the feed. Mix thoroughly with the hands and pour over the mixture of drug and feed a well mixed solution containing 50 cc. of warm water and 50 cc. of corn syrup (Karo Blue Label).
  - C. If the drug is soluble in water, the requisite amount of drug is dissolved in 50 cc. of warm water. Add 50 cc. of corn syrup, mix well and pour the mixture over the dry pellets.

In preparing the pellet form of the feed, it is important that, after the syrup solution has been added to the pellets and the feed has been thoroughly mixed, the feed be spread evenly over the surface of a flat pan and permitted to dry at room temperature until the surface of the pellets is slightly tacky.

We have observed that when the pellet form of the rabbit chow is made up according to the preceding directions, guinea pigs eat the mixture readily, consuming at least 45 to 55 g. of the feed each twenty-four hours (we use guinea pigs weighing at least 450 g.).

An important feature in the foregoing method of preparing the pellets is that the moisture content is not in excess; otherwise the pellets have a tendency to soften. A sufficient amount of the mixture described can be made to take care of the feed required for two to three days. During warm, humid weather there may be a tendency of the mixture to mold. If this happens, it is desirable to prepare the feed daily for each day's requirement.

*Proskauer and Beck Synthetic Medium*

(Vorwald's Modification)

Monopotassium phosphate.....	5 g.
Asparagine.....	5 g.
Magnesium citrate.....	2.5 g.
Magnesium sulfate.....	0.6 g.
Glycerol.....	20 cc.
Distilled water.....	1,000 cc.

Adjust pH to 7.8.<sup>7</sup>

Autoclave at 10 pounds pressure for twenty minutes.

Filter, dispense in 100 cc. amounts in flasks of 250 cc. capacity and autoclave at 10 pounds pressure for twenty minutes.

## Note:

1. "Difco" asparagine is recommended for use in the preparation of this medium.
2. To the cold or lukewarm, distilled water (1,000 cc.) add and dissolve, in the order given, each of the crystalline substances.
3. Use a 40 per cent solution of sodium hydroxide in distilled water for adjusting the hydrogen ion concentration.
4. Adhere rigidly to the time and temperature given for sterilization. Each period that the solution is in the autoclave should not exceed thirty minutes.
5. After the first period of autoclaving, the solution should be cooled to 60° C., and not shaken, and filtered immediately.
6. Transplants should be made every two to three weeks. This is important. As the cultures get older and more luxuriant and the mass of bacterial cells becomes more and more submerged, difficulty is encountered in getting the transplanted material to float on the surface of the liquid medium. Growth at the surface must ensue if the transplants are to succeed.

## SUMMARY

An outline of the essential procedures utilized in this laboratory for testing antituberculosis substances is presented. The methods suggested are based on the premise that the chemotherapeutic attack should be directed primarily toward tuberculosis as a disease in addition to the attack against the bacteria which initiate the morbid state. For this reason the *in vivo* procedure is considered more reliable than procedures *in vitro*. For the preliminary or screening test, medication is started when the infective agent is introduced and the experiment is terminated sixty days later. Substances considered worthy of a more exacting test are subjected to a procedure in which true chemotherapeutic conditions prevail. In this latter or crucial test, treatment is started six weeks after the guinea pigs have been inoculated and is continued until most, if not all, of the untreated controls have died. Nearly five years' experience has indicated that

<sup>7</sup> Recently, following the suggestion of Dr. Guy P. Youmans, Medical School, Northwestern University, we have adjusted the pH to 7 and have observed a more rapid and vigorous growth of transplants of H37RV than when the pH was 7.8. Doctor Youmans also suggested substituting potassium sulfate for magnesium sulfate. This precludes the formation of a precipitate; consequently it is necessary to autoclave the medium only once rather than twice.

the procedures described are practical and the results are capable of being duplicated. Consideration is given to the selection and care of the animals, the infective inoculum, administration of test substances and recording of results. The critical requirements for a satisfactory chemotherapeutic agent for combating experimentally induced tuberculosis in animals are given.

#### SUMARIO

Bosquéjense los procedimientos esenciales utilizados en el laboratorio de los autores para comprobar sustancias antituberculosas. Las técnicas propuestas b́asense en el principio de que el ataque quimioteraṕutico debe encarar primordialmente la tuberculosis como enfermedad, aparte del ataque dirigido contra las bacterias que inician el estado morbosos, por cuya raz3n el procedimiento *in vivo* se considera ḿas fidedigno que los procedimientos *in vitro*. Para la prueba preliminar o de triaje, iníciase la medicaci3n cuando se introduce el agente infectivo y se termina el experimento 60 d́as despu3s, somet\_iéndose las sustancias que se consideren dignas de una prueba ḿas rigurosa, a un procedimiento que reuna verdaderas condiciones quimioteraṕuticas. En esta ultiima prueba, o sea la decisiva, iníciase el tratamiento seis semanas despu3s de inocular los cobayos y se continúa hasta que haya muerto la mayoría de los testigos no tratados, si no todos. Una observaci3n de casi cinco ańos indica que los procedimientos descritos son pŕacticos y los resultados capaces de ser duplicados. Préstase consideraci3n a la selecci3n y cuidado de los animales, al in3culo infectivo, a la administraci3n de sustancias de ensayo y a la anotaci3n de los resultados. Exp3nense los requisitos fundamentales que debe cumplir un agente quimioteraṕutico satisfactorio destinado a combatir la tuberculosis experimental en los animales.

#### REFERENCE

- (1) FELDMAN, W. H.: Scheme for numerical recording of tuberculous changes in experimentally infected guinea pigs, *Am. Rev. Tuberc.*, 1943, 48, 248.

## AMERICAN TRUDEAU SOCIETY

### Report of the Wisconsin Trudeau Society

Dr. John D. Steele, *Secretary*

A regular meeting of the Wisconsin Trudeau Society was held at the Wisconsin State Sanatorium, Wales, on Saturday, March 24, 1945. The Society was entertained at lunch by the Sanatorium. In the absence of the president and the vice-president, who are in the Armed Forces, Dr. R. H. Schmidt, Jr., Superintendent of the Wisconsin State Sanatorium, presided. Forty-two members registered.

The following program was presented:

*Pleurisy with Effusion* by Paul E. Pifer, M.D., Kenosha.

The various etiological factors of pleurisy with effusion were discussed. It was pointed out that "idiopathic" pleurisy with effusion should be considered tuberculous until proved otherwise.

*Some Things Learned from a Statistical Analysis of 5,000 Wisconsin Sanatorium Admissions* by Harold Holand and A. A. Pleyte, M.D., Milwaukee.

An analysis of 1,731 admissions to twenty Wisconsin sanatoria in 1942, and 729 tuberculosis deaths of Wisconsin residents, indicated that: (1) The ratio of patients admitted to deaths in older age groups is far lower than in younger age groups. (2) The tuberculous patients among these older groups present markedly more advanced disease and appear to be more infectious than younger patients. (3) The ratio of the number of patients treated to the number of deaths, and the proportion of minimal admissions, is higher in counties having a sanatorium within their boundaries than in non-sanatorium counties. (4) The proportion of minimal admissions is twice as high among first admissions as among readmissions. (5) The proportion of undetermined diagnoses is considerably lower and the proportion of minimal cases considerably higher among patients with a known family history of tuberculosis than among patients without such history.

*Criteria for Determining Arrest in Pulmonary Tuberculosis* by John K. Shumate, M.D., Madison.

A summary of 193 cases of proved active pulmonary tuberculosis on admission who were discharged as arrested and adequately followed up during a recent five-year period was presented. Methods of determining arrest in use were discussed. Twenty-six per cent of all cases relapsed. It was concluded that present national standards seem lax in examination of bronchial secretions and it is doubtful that cases under pneumothorax treatment should be considered arrested.

*The Accuracy of Cultures of Pulmonary Secretions in the Evaluation of Activity in Pulmonary Tuberculosis* by L. L. Sanford, M.D., Wauwatosa.

In evaluating the accuracy of the examination of pulmonary secretions in determining activity in pulmonary tuberculosis, the records of 2,248 consecutive patients admitted to Mairdale Sanatorium over a five-year period were reviewed. In active reinfection tuberculosis it was found that direct and concentrated smears of pulmonary secretions showed an accuracy of only 80 per cent. However, when cultures were also used, it was found that only slightly less than 1 per cent of all patients with X-ray evidence of activity could not be proved positive.

*The Diagnosis of Boeck's Sarcoid* by Helen A. Dickie, M.D., Madison.

Hilar adenopathy alone or stringy, nodular symmetrical parenchymal lesions associated with varying degrees of hilar enlargement should arouse the suspicion of Boeck's sarcoid. The association of parotitis, uveitis and erythema nodosum with the above is very significant. In the absence of proof by biopsy, a negative tuberculin, elevated serum globulin, cystic changes in the small bones, absence of fungi or tubercle bacilli on gastric cultures, and the benign course are valuable confirmatory evidence.

*Roentgen Therapy in Boeck's Sarcoid* by Elizabeth Clark, M.D., Madison.

Sixteen cases of pulmonary sarcoidosis have been treated in the Department of Radiology at the State of Wisconsin General Hospital. Favorable results have been obtained in 11 of these on which follow-up studies were available. Roentgen therapy was therefore suggested as a means of shortening the course of the disease.

*The Relation of Tuberculous Tracheobronchitis to Menstruation* by George H. Jurgens, M.D., Wauwatosa.

A group of 158 female patients was followed closely for symptomatic changes possibly associated with menstruation. It was concluded that there is an association between ovarian function and certain symptoms in pulmonary tuberculosis. These symptoms were found to vary in degree and to occur more frequently when gross lesions in the tracheobronchial tree were present.

It was resolved that the following suggestions be submitted by the Wisconsin Trudeau Society to the Committee appointed to revise *Diagnostic Standards*.

I. The discharge classification should be changed to the following:

1. Active
  - a. Dead
  - b. Improved
  - c. Unimproved
  - d. Worse

## 2. *Inactive*

The X-ray findings in serial films are those of a stationary or healed lesion. The pulmonary secretions are negative as noted below in II and III. The period of inactivity shall date from the time that these conditions have existed, for example, inactive one year, two years, ten years, etc.

- II. Sputum should not be considered as negative unless a series of acceptable authentic specimens has been found negative on culture or guinea pig inoculation.
- III. When a patient is not raising or when there is any question as to the authenticity of expectorated sputum specimens, a series of fasting gastric aspirations should be performed, the gastric contents cultured or inoculated into a guinea pig and found negative before such a patient can be classified as "inactive."

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# THE AMERICAN REVIEW OF TUBERCULOSIS

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## ABSTRACTS

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ABST. No. 1

**Acute Diffuse Fibrosis of Lungs.**—Four cases of pulmonary disease are described, all presenting new, and thus unusual, clinical pictures. Although the symptoms of each case differed somewhat from those of the others, they bore such a striking resemblance, that having seen 2 cases, the correct diagnosis was suggested when the third appeared. The anatomical picture was one equally unfamiliar. The lungs were the seat of a wide-spread connective tissue hyperplasia throughout the interstitial structures. The alveolar walls were tremendously thickened; in the early stages of the process crowded with fibroblasts which, at later stages, were replaced by mature scar tissue. It is noteworthy that the alveoli themselves contained little or no cellular inflammatory exudate in contrast with that which is seen in pneumonia. These pulmonary changes caused an extreme degree of dyspnoea and cyanosis, and, after a matter of only a few weeks, led to dilatation and hypertrophy of the right ventricle of the heart so that at the end, in at least one patient, grave symptoms of myocardial insufficiency developed. From the pathological anatomy and the symptoms of these 4 patients, a clinical picture of an uncommon and remarkable disease may be reconstructed. Pulmonary inflammation of the peculiar type described develops insidiously with little local or constitutional disturbance. There are none of the symptoms which usually mark the advent of bronchopneumonia; there is little fever, the patients are not incapacitated or forced to bed, the leucocytes are little if any

increased. Very shortly after the onset, connective tissue begins to proliferate within the alveolar walls, and soon dyspnoea comes on and grows increasingly severe as a result of the disturbance of the relation of the capillaries to the alveolar lumen, and the gradual compression of alveolar spaces by the rapidly advancing fibrosis. Two patients died of slowly progressive suffocation. If this stage of the disease is outlived there is increasing evidence of myocardial insufficiency. As pulmonary fibrosis increases and spreads, the circulation in the lungs is impeded, the pressure in the pulmonary artery is increased, and soon the right ventricle becomes dilated and hypertrophied. In 3 of the 4 cases, the right ventricle was appreciably enlarged and its walls thickened, although in one case only forty-six days had elapsed from the onset of symptoms to the time of death and in another only thirty-one days. As the pressure in the pulmonary circulation steadily rises a constantly increasing burden of work is thrown upon the right side of the heart, and sooner or later the symptoms of congestive heart failure appear and steadily advance until finally death occurs from myocardial insufficiency. It is believed, however, that patients may recover from localized forms of this disease. About the cause of this disease nothing is known. The absence of organisms suggests a viral aetiology. The possibility of a chemical irritant has, however, to be considered. (Illustrated.)—*Acute Diffuse Interstitial Fibrosis of the Lungs*, L. Hamman & A. R. Rich, *Bull. Johns Hopkins Hosp.*, March, 1944, 74: 117.—(J. S. Woolley)



**Oil Aspiration Pneumonia.**—Twenty cases of oil aspiration pneumonia were diagnosed clinically within a period of seven months at Welfare Hospital for Chronic Disease in New York City. Autopsy confirmation was obtained in 5 cases. A review of 300 consecutive autopsies disclosed 13 additional cases not included in the report. Some of these cases might have been diagnosed antemortem if the condition had been borne in mind. Among the 20 cases the sexes were equally divided; all were adults ranging in age from twenty-six to eighty-two years. An accompanying disease contributing to the aspiration of oil was present in all instances. The patients could be classified into three groups: neurological, cerebrovascular and arthritics. In the neurological group, there were 6 cases of multiple sclerosis, one spastic pseudosclerosis, one Little's disease and one cerebellar syndrome. There were 4 hemiplegics in the cerebrovascular group. In the third group were 7 patients with advanced chronic rheumatoid arthritis; one in this group also had an accompanying Parkinson's syndrome. The predisposing and contributing factors in the development of oil aspiration pneumonia were the accompanying dysphagia, weakness and debility. The most common causative agent was liquid petrolatum given for constipation. A positive history of having taken considerable quantities of liquid petrolatum was obtained in 12 cases. The oil intake was usually an ounce, either daily or every second or third day, over a period of from two months to two years. Two cases, obtaining vitamin therapy, received wheat germ oil frequently for a period of one to two months. In 6 cases, no history could be obtained of receiving any specific oils. Nevertheless, the roentgen examination of the chests revealed changes suggestive of oil aspiration pneumonia. One case was proved at autopsy. All patients received considerable quantities of milk daily; this may have been a factor in some of the cases. A diagnosis of oil aspiration pneumonia should be considered in dysphagic and debilitated patients whenever serial roentgenograms reveal evidences of a protracted bron-

chopneumonia, even when no history of oil ingestion is obtainable. Clinical signs and symptoms may be of little or no value. In some cases no signs or symptoms were elicited, while in others a few moist râles at the bases, and dulness were present. A few patients had a low grade fever; a higher temperature usually indicated a superimposed acute bronchopneumonia or some other infection. The roentgen examinations revealed an increase in the size, number and density of the lung markings, which had a tendency to become confluent. The root shadows were enlarged. Acinous and lobular shadows were present. Some were confluent, forming larger areas of consolidation. The diminution in aeration depended upon the extent of involvement. The peripheral portions of the lungs were not involved. These were superimposed upon diffuse interstitial changes. The findings were persistent and showed little or no regression. Progression was manifest with continued oil administration. A superimposed bronchopneumonia may be present which may resolve. The diagnosis of oil aspiration pneumonia should always be considered when, on serial studies, there are evidences of a protracted bronchopneumonia in an individual with a history of oil administration and dysphagia. The incidence of oil aspiration pneumonia will be reduced if the use of oily medications and liquid petrolatum is kept at a minimum, or discontinued in the aged, bedridden, debilitated, and those suffering with dysphagia.—*Oil Aspiration Pneumonia, M. Moel & H. K. Taylor, Am. J. Roentgenol., February, 1943, 49: 177.*—(W. H. Merrit)

**Echinococcus Cyst.**—Echinococcus disease is rare in North America, but in the past decade certain valuable diagnostic and prognostic features in the roentgen examination have been described. A case is reported and the historical aspects of the disease, first described by Béchère, discussed. Cysts may change shape during respiration and large cysts tend to produce enlargement of the portion of the thorax in which they lie, resulting in some displacement of the mediastinal struc-

tures to the opposite side. They are not always sharp in outline, due to inflammation and varying degrees of atelectasis in the adjoining lung. As hydatid cysts enlarge a bronchial communication may develop in the adventitia surrounding the cyst so that, upon coughing, air may enter the potential space between the membrane of the hydatid vesicle and the adventitia. Although this is rarely seen with echinococcus cysts, when it is found it is pathognomonic. When the cyst membrane becomes detached, death of the parasite presumably occurs. Frequently when the cysts rupture they become infected and the membrane may be seen floating in the fluid. At times expectoration of the cystic fluid and membrane may occur resulting in spontaneous cure.—*Echinococcus Cyst of the Lung*, W. A. Evans, *Radiology*, April, 1943, 40:362.—(G. F. Mitchell)

**Infected Lung Cyst.**—Cystic disease of the lung is now more frequently recognized and new advances in thoracic surgery have made possible curative procedures so that the importance of diagnosis has been enhanced. More recently a practical aspect of lung cysts has been described, namely, their relationship to chronic pulmonary suppuration. Maier and Haight elaborated on this and also have stressed the importance of obtaining a biopsy from the wall of any fluid pocket in the chest, usually at the time of drainage. The true cyst develops from a bronchial bud. Therefore, any bronchial communication may be open or closed so that the cyst may contain fluid, fluid and gas or gas alone. If the patency of the communication varies from time to time, contents of the cyst may also change. The presence of a bronchial communication may lead to the development of infection within the cyst producing the signs and symptoms of pulmonary abscess or encysted empyema. The diagnosis may be difficult. If, in addition to the finding of pus on thoracentesis, there is a history of repeated pulmonary infections presumed to be pneumonia, or of repeated drainage of a fluid pocket without permanent result, the possibility of in-

fecting lung cyst should be considered also. Fungus infections can usually be excluded by bacterial study, but biopsy at the time of drainage is the best method of exclusion of lung cyst. It is possible that some chronic recurring encapsulated empyemata may be infected lung cysts. From the roentgenological point of view, the finding of a sharply encapsulated, well defined pocket standing out separately from the remainder of the chest, the absence of pleural thickening, a low position of the area, the absence of retraction of mediastinum or diaphragm toward the encapsulated pocket, and the finding of a relatively thin wall when the pocket contains air should suggest the possibility of a lung cyst. The demonstration of trabeculae within the cyst is also important. Biopsy of the wall at the time of drainage is the best means of diagnosis. Radical surgery, preferably lobectomy, is the best procedure for obtaining a permanent cure. Cases are reported illustrating the (1) development of a bronchial fistula in a fluid-filled cyst, (2) multiple infected cysts simulating loculated empyema or lung abscess, (3) two single large cysts simulating an encapsulated empyema, and (4) eventual development of gas-containing cysts seen at birth into multiple pus-filled pockets simulating lung abscesses.—*Infected Lung Cyst*, L. G. Rigler, *Radiology*, May, 1943, 40:485.—(G. F. Mitchell)

**Treatment of Solitary Pulmonary Cysts.**—The author presents 7 cases of solitary pulmonary cysts. Roentgenologically the appearance was varied, depending upon the complications. The classical thin-walled empty cyst without surrounding infiltration and fluid level was seldom seen. More often it was complicated by infiltration and fluid level within the cyst, surrounding infiltration, pneumothorax with or without empyema or fluid, and at times the cyst was full and was seen as a dense, oval-shaped, clearly defined mass. Six of the 7 cases presented themselves for treatment—and in each case attention was focused upon the cyst by some accident or complication: (1) infection; (2) infection with

rupture, causing pyopneumothorax; (3) rupture without infection, causing a tension pneumothorax; (4) rupture with discharge of sterile fluid into the pleural cavity; (5) progressive ballooning-out of the cyst. Of the 6 cases operated on (the seventh was asymptomatic and did not come to operation), 4 represented congenital cysts of pulmonary origin and, of these, 2 were cystic accessory lobes. Of the other 2, one was probably an emphysematous bulla, and the sixth case originally was probably lung abscess. The treatment of asymptomatic or silent cysts is also discussed. In contrast to Singer, Eloesser and Maier, the author believes asymptomatic cysts are uncommon, are too exposed to complications and should be operated on if possible. The surgical treatment consists of extirpation, lobectomy, or pneumonectomy. Preoperatively, drainage of empyema or infection within the cyst cavity may be necessary. Drainage postoperatively is advised if the cyst has been opened into. Complete expansion of the lung is striven for, and one or two pleural aspirations may also be necessary following lobectomy or pneumonectomy.—*The Surgical Management of Solitary Cysts, or Cyst-like Structures, of Pulmonary Origin*, M. D. Tyson, *Ann. Surg.*, July, 1943, 118: 50.—(D. J. Rednor)

#### Roentgen Treatment in Chronic Asthma.—

One hundred consecutive cases of asthma were given courses of roentgen therapy. A cross-fire technique, employing 2 anterior, 2 posterior and 2 lateral portals, was used with average total dosage of between 800 and 1600 r administered through the 6 portals. Most of the patients expectorated variable amounts of mucus. Within a period of three days to three weeks most individuals coughed up large amounts of thick, stringy purulent mucus, oftentimes pitted with plugs, and usually in greater amounts than had previously occurred. In practically all cases where the individual was able to rid himself of large amounts of mucus, improvement was almost instantaneous and proportionate to the amount brought up. Generally within two or three weeks the

expectoration of mucus had entirely ceased and, along with this change the patient became free of asthma. During the first year of observation, 35 patients were given two courses of therapy and 15 patients three courses of therapy; the remaining 50 received a single course. The amount of radiation given is within a safe range of dosage and could be repeated yearly over a period of eight to ten years without damaging the skin or producing pulmonary fibrosis. The results were considered excellent in 39 patients, good in 40, fair in 13, poor in 6, and insignificant in 2. The good results were obtained in cases showing infection in the bronchial tubes or paranasal sinuses or both. Radiation therapy in asthmatic sufferers free of infection seems to have little or no effect. All patients were given 5,000 units of vitamin B1 daily by hypodermic injection for control of nausea following the radiation therapy.—*The Therapeutic Value of Roentgen Treatment in Chronic Asthma*, W. M. Hull, R. M. Balyeat & L. K. Chont, *Am. J. Roentgenol.*, February, 1943, 49: 227.—(W. H. Meritt)

**Pathology of Bronchial Asthma.**—A uniform pathological picture in deaths from bronchial asthma is not found at the autopsy table. In some cases a definite pathological diagnosis can unhesitatingly be made, because there is a very characteristic picture. However, this picture may be absent in patients who undoubtedly were correctly diagnosed clinically as asthmatics and who died a typical suffocation death. In these cases hypersecretion of thick mucus must have been the cause of the asthmatic seizures. When the characteristic picture is present the main seat of morphological alterations is in the bronchi, both large and medium, and in the bronchioli. The bronchioli may contain spirally wound mucous threads which form the nuclei of Curshman's spirals. Apparently these threads may be formed by the surface epithelium alone in the absence of mucous glands. The medium and larger bronchi contain an abundance of thick mucus and Curshman's spirals, and the epithelium shows

advanced degeneration. The walls of the bronchi participate in the changes. The basal membrane shows hyaline thickening, the submucosa is oedematous, the capillaries are dilated, and the tissue is infiltrated with numerous cells, mainly eosinophils, lymphocytes and plasma cells. The longitudinal elastic membrane and the circular muscular coat are markedly hypertrophied probably as a result of bronchospasm. The mucous glands show dilatation and herniate into the lumen of the bronchus. The peribronchial wall also shows a heavy infiltration of eosinophils and other cells. The lungs commonly show emphysema and atelectasis, and the right heart may be enlarged.—*Zur pathologischen Anatomie des Asthma bronchiale*, C. Wegelin, *Schweiz. med. Wchnschr.*, January 8, 1944, 74: 8.—(H. Marcus)

**Disability in Silicosis.**—In industries where there are dust hazards preemployment records should be obtained containing the family history, especially regarding tuberculosis, clinical history, occupation history, record of physical examination including lung function tests and X-ray report. The roentgenogram should be of excellent and constant quality and the consultant should be familiar with the type of work and the dust hazard of the work for which the men are employed. The criteria for the rejection of applicants for jobs entailing a silica hazard on the basis of preemployment films are (1) inactive pulmonary tuberculosis, (2) extensive primary tuberculosis in persons under thirty, (3) primary tuberculosis of questionable stability, (4) inactive adult type tuberculosis, (5) suspected silicosis especially with a history of exposure, (6) emphysema and (7) other pathological findings of known or unknown aetiology making the applicant an unfavorable risk. When employed, a careful record of absenteeism with special reference to pulmonary illness should be kept, routine check-ups done and X-ray films made, and, when indicated, lung function tests repeated. Roentgen evidence of disability is often unreliable and inaccurate, for uncomplicated silicosis associated with

moderate fibrosis may be more disabling than massive lesions. According to work done by Irwin, this may be due to the fact that more dyspnoea is produced by thickening and fibrosis of the alveolus itself than by the nodular fibrosis. When the X-ray film shows superimposed infection, disability should be anticipated and with roentgen evidence of active tuberculosis present one may state that disability is total and permanent. The diagnosis of superimposed tuberculosis may be difficult and should be confirmed by laboratory tests and serial films. The author concludes that disability in industrial lung diseases cannot be accurately estimated by X-ray examination alone.—*Correlation of Disability with Roentgen and Clinical Findings in Silicosis*, P. Bovard, *Radiology*, July, 1943, 41: 11.—(G. F. Mitchell)

**Disability in Silicosis.**—Since disability in silicotics varies greatly and cannot be estimated by roentgenograms such disability must be estimated in terms of altered function of the lungs. Respiratory function tests are of two main types, those made with the patient at rest and those obtained during exercise. The former include determination of vital capacity, complementary air, tidal air, reserve air, functional residual air and residual air. Examinations of the patient during exercise are probably more practical and less complicated, since disability is measured in percentage of work ability. These tests include respiratory rate and amount of air breathed before, during and after exercise. A bicycle ergometer is used for this work, the subject pedaling at the rate of 20 miles per hour. Normal persons get more air during exercise by an increase in the depth of respirations, while a person with respiratory disability can only obtain required air by an increase in the rate of respirations.—*Correlation of Disability with Roentgen and Clinical Findings in Silicosis: Part II*, J. W. G. Hannon, *Radiology*, July, 1943, 41: 13.—(G. F. Mitchell)

**Pneumoconiosis in Boiler-scalers.**—The composition of scale within boilers consists

mainly of iron, sodium, magnesium and calcium as chlorides, sulfates and phosphates, and of an insoluble silica residue. The diagnosis of the disease can only be made by an occupational history and X-ray examination. The physical signs and complaints are those associated with pulmonary fibrosis and reduction in respiratory efficiency. A case report is given of a forty year old man who worked as a boiler-scaler for fourteen years, beginning at the age of eleven.—*Pneumoconiosis in Boiler-scalers*, P. G. Todd & D. Rice, *Lancet*, March 4, 1944, 246: 309.—(H. Marcus)

**Lung Changes in Welders.**—Electric arc welding which is done in large rooms and where the fumes are not allowed to concentrate excessively near the breathing level does not cause any lung changes even after many years of work. Excessive inhalation of concentrated fumes, especially in confined and unventilated spaces, may cause siderosis in the lungs in from six to ten years. The siderosis so produced consists only of inert iron pigment deposits in the lymphatics, without fibrous tissue proliferation and without progressive changes after exposure is materially decreased. Electric welding or siderosis do not predispose to tuberculosis or other lung infections. The siderosis of welding causes no functional impairment of the lungs and, therefore, no symptoms referable to the lungs. Acute irritative phenomena of the throat may occur with too prolonged confined work in dense clouds of fumes, but these appear to be transitory reactions leaving no residual impairment. Any respiratory involvement may be prevented in welding, even with the most confined and prolonged work, if proper precautions are taken, either by adequate exhaust ventilation, ventilated helmets or positive pressure respirators.—*Further Observations on Lung Changes in Electric Arc Welders*, O. A. Sander, *J. Indust. Hyg. & Toxicol.*, March, 1944, 26: 79.—(G. C. Leiner)

**Dust Hazard in Tremolite Talc Mining.**—A study of the tremolite talc mining and

milling industry in northern New York State is reported. Talc, a hydrous magnesium silicate, in this region is of the fibrous variety known as asbestine; it is mingled with two other fibrous silicates, tremolite and anthophyllite. Analysis of material from both mines and mills gave consistently a free silica content of 1 per cent or less. Microscopical studies of dust showed fine, straight needle-like fibres. Dust counts in mining ranged from 6 to 5,000 million particles per cu. ft.; in milling, from 20 to 215 million particles per cu. ft. In a group of 221 tremolite talc miners and millers advanced pulmonary fibrosis was found in 32 men (14.5 per cent). All cases of fibrosis occurred among those men who had worked in tremolite talc for ten years or longer (107 men) giving an incidence for this group of 29.9 per cent. Eighteen cases were selected for special study because these men had never worked in any other dusty industry. Thirteen of the 18 had one or more symptoms referable to the lungs. Ten complained of dyspnoea, 7 of chronic cough and 3 of chest pain. Five complained of excessive fatigue. All 18 showed limited chest expansion. Thirteen showed abnormal lung signs and 13 showed curving of the nails or clubbed fingers. Cardiac hypertrophy was observed in one case and auricular fibrillation in another. The group tended to present an undernourished and drawn appearance. Dyspnoea was unusually pronounced in relation to the extent of the fibrosis seen in the roentgenograms. The type of fibrosis seen in the roentgenograms was very fine and diffuse, frequently showing an appearance of soft haziness to which the term "ground glass" used in describing certain cases of asbestosis could be applied. In a number of cases there was, in addition, a distinctly granular appearance and in some nodulation which might be confused with silicosis. In certain films soft conglomeration also occurred. The fibrosis tended to be more marked on the right side, the mid-portions of the lungs and the bases. The hilar nodes showed a slight or moderate increase in density. Evidence of obliterative pleuritis and emphysema was also

present in some cases. In some a blurring or "shagginess" of the cardiac outline was noticeable. The incidence of healed primary and reinfection type tuberculosis was the same as in other industrial groups. In the total group of 221 talc workers there were 29 (13.1 per cent) cases of healed primary tuberculosis and 6 (2.7 per cent) cases of healed reinfection type tuberculosis. Five cases (2.2 per cent) were considered, on the basis of the roentgenographic appearances alone, to show clinically significant tuberculosis. This is slightly higher than the average rate in industrial groups of about 1.2 per cent. Among the 18 cases of fibrosis in men exposed only to talc, clinically significant tuberculosis appeared to be a complicating feature in 3 cases (16.6 per cent). A most interesting finding was the presence in 14 instances (6.3 per cent of the 221 talc workers originally examined roentgenographically) of what appeared to be deposits or plaques of opaque material (perhaps talc or calcium) on the visceral pleura, including the region of the diaphragm and occasionally the pericardium. The plaques varied in size from a single, linear-appearing deposit of a few centimeters in length in the region of the diaphragm to massive deposits bizarre in shape, extending over a large part of the lung fields. They were characterized not only by irregularity of shape, but by marked variations in degree of density, and by sharpness of their borders. So far as can be ascertained, previous infection played no rôle in their production. The underlying lung tissue showed fibrosis in some cases. When this fibrosis was absent there was no associated enlargement of the hilar nodes. There were no signs or symptoms attributable to the plaques. Gardner attributes fibrosis in tremolite talc workers to the contaminating presence of free silica, but inasmuch as the free silica content of the twelve samples of mineral from talc mills and mines analyzed in the present study was found to be practically negligible (less than 1 per cent) it seems reasonable to suppose that the fibrosis observed in these cases is primarily the result of inhalation of the silicates. Microscopical

study has shown that this dust is largely fibrous in character, and it may be that this physical characteristic is responsible for the pathology of tremolite talc fibrosis. The possibility of action analogous to that which occurs in asbestosis is suggested by several facts: (1) the chemical and physical similarity between the minerals in this area and those found in asbestosis; (2) the disability in tremolite talc fibrosis, like that in asbestosis, tends to be greater than would be expected from the extent of the lesion as seen in the roentgenogram. Roentgenologically the talc fibrosis resembles early asbestosis in its fineness, diffuseness and "ground glass" quality; in addition, asbestosis cases may show a mottled or nodular appearance similar to that seen in the more advanced cases of talc fibrosis. One conspicuous dissimilarity between asbestos and talc dust is the absence of any change resembling "talc plaques" in the lungs of asbestos workers. The writers conclude that tremolite talc is a silicate dust, capable, like asbestos, of causing a disabling pneumoconiosis.—*The Dust Hazard in Tremolite Talc Mining: Including Roentgenological Findings in Talc Workers*, W. Siegal, Adelaide R. Smith & L. Greenburg, *Am. J. Roentgenol.*, January, 1943, 49: 11.—(W. H. Meritt)

✓ **Bagassosis.**—A thirty-two year old Negro male developed, three weeks prior to his hospital admission, cough, productive of clear, mucoid sputum, weakness, malaise. One week prior to his admission he started to suffer from dyspnoea and fever. For the past eight months his work had consisted first in moving bales of damp cane grindings from the sugar house to the fields, later in moving the dry bagasse from the fields to the railroad cars. On physical examination the only abnormal findings were fine râles over the right lung base. X-ray examination showed miliary infiltrations throughout both lungs. After twenty days, slight clearing was seen on the roentgen picture, and further clearing was noted in the subsequent five months. No tubercle bacilli were found in the sputum. From these findings and from the history the

diagnosis of bagassosis was made. It is pointed out that bagassosis may be contracted even when working out of doors with the dried material and that recovery may occur over a period of a few months.—*Bagassosis: A Case Report*, S. Chaille Jamison, Margaret Strange Bryan & Jane Matthews Day, New Orleans M. & S. J., January, 1944, 96: 291.—(G. C. Leiner)

**Tobacco and Pulmonary Disease.**—In the past, heavy tobacco smoking has been indicted for postoperative pulmonary complications but statistical proof was lacking. A study of 1,257 consecutive cases of abdominal operations in adults provides the statistical background of this communication. The cases were unselected, and included both men and women. The operations included are simple appendectomies, and drainage of appendiceal abscesses, herniotomies, pelvic operations on women, midabdominal operations, upper abdominal operations, and genitourinary operations. The anaesthesia was of the closed circuit type with nitrous oxide and oxygen and minimal amounts of ether. The premedication was either atropine, or an omnopon scopolamine mixture. Atropine showed a slight tendency towards lessening the pulmonary complications, but statistically the difference was not significant. The patients were divided into smokers, light smokers and nonsmokers. Naturally there were many more smokers in the male group than in the female group. It was uniformly demonstrated that smokers showed the highest incidence of pulmonary complications, a total rate of 58 per cent in men for all types of operations. These figures include bronchitis, bronchopneumonia and atelectasis, but the number of patients who really showed constitutional symptoms of respiratory tract disease was, of course, much smaller, namely 9 per cent in men and 4 per cent in women. In all types of operations on the abdomen, men showed a higher incidence of complications than women, namely 41 per cent as compared to 13 per cent. Men over forty-one years of

age tend to have more chest complications than the group under forty. It is felt that complications will be avoided if heavy smokers cease smoking a few days before operations. The greater sex incidence in men is explained by the man's greater reliance on diaphragmatic breathing normally than the woman's, and it is just this diaphragmatic breathing that is most interfered with following abdominal operations, especially operations on the upper abdomen. Also, the type of work usually performed by men, together with the chronic infection of the respiratory passages due to smoking are believed to contribute to their greater morbidity.—*Tobacco Smoking and Pulmonary Complications after Operation*, H. J. V. Morton, *Lancet*, March 18, 1944, 246: 368.—(H. Marcus)

**Air Pollution and Respiratory Diseases.**—Mills analyzed the mortality rates from pneumonia, tuberculosis and various types of cancer of the upper and lower respiratory passages in relation to the concentration of soot fall in the Cincinnati and Pittsburgh environs. Both these cities have large industrial populations in immediate proximity to the Ohio river where the soot fall is heavy and where the air is heavily polluted by carbonaceous and siliceous particles and settlements on the neighboring hills where this air pollution is much less. He found a highly significant correlation between atmospheric pollution and respiratory disease death rates in the various districts of the above two cities. The men living and working in these badly polluted districts are particularly affected, among whom respiratory disease is two to three times more prevalent than among those living in the neighboring hilltop districts where the air pollution is much less. That this difference in mortality from respiratory diseases is not due to mere socio-economic differences of these two populations is indicated by the fact that females living in the polluted air have an incidence of pneumonia and tuberculosis which is only about 50 per cent greater than females living in the hills, whereas amongst

males this difference between the two populations is about 100 per cent. In the rural districts of these two cities, on the other hand, little difference exists between the rates for males and females. Exhaust steam from power sources adds greatly to the winter smoke problem by remaining as a fog which holds flue products suspended in the air. Mills recommends the use of low volatile coal, effective trapping of the silica carrying fly-ash from chimneys, preliminary washing of high sulphur coal and the use of Diesel or electric power by railroads within metropolitan limits.—*Urban Air Pollution and Respiratory Diseases*, C. A. Mills, *Am. J. Hyg.*, March, 1943, 37: 131.—(M. B. Lurie)

**Spontaneous Pneumothorax.**—Thirty-one cases of idiopathic spontaneous pneumothorax, found in the literature between the years 1935 and 1940, and 13 new and never reported cases are analyzed. The age of the patients at the time of the attacks was between fourteen and fifty years, the average being twenty-seven to twenty-nine. There were 38 males and 6 females. The right lung was affected in 18 cases, the left in 24; both lungs simultaneously in one; first the right, then the left in one. Only 15 had any chest disease in the history. Symptoms were: chest pain in 36 cases, cough in 3, dyspnoea in 26, vomiting in 6. Five patients had primarily abdominal symptoms. Occupation or strain has no significance. In 6 patients the attack occurred during sleep. Signs of pneumothorax were present in 41 cases. Other findings were: fast pulse, dyspnoea, shock, fever, cyanosis. In 16 patients there was a rise of the white blood cell count up to 36,900. Findings on X-ray examination were: displaced mediastinum in 12 cases, complete lung collapse in 2, fluid in 10, bullae in 5, adhesive bands in 2, pneumonic process in one, emphysema in soft tissue in one, fibrous change in one, old pleurisy in one, calcified lymph nodes in one. Ten patients had repeated attacks. One patient died; all the others recovered. The time of reexpansion

was a few days to two years.—*Idiopathic Spontaneous Pneumothorax*, S. H. Babington, *West. J. Surg.*, February, 1944, 52: 73.—(G. C. Leiner)

**Chronic Empyema.**—An empyema is considered chronic when the size of the empyema cavity remains stationary and when the healing process becomes so slow that it is hardly noticeable. An acute empyema becomes chronic due to (1) bronchopleural fistula, (2) inadequate drainage, (3) tuberculosis, (4) too late draining, (5) bronchiectases. Surgical procedures are: (1) establishment of adequate drainage; (2) decortication of the lung; (3) thoracoplasty; (4) Schede operation, which is the ideal operation in chronic nontuberculous empyema. Tuberculous empyema is a complication in about 10 per cent of pneumothorax cases. If a tuberculous empyema does not improve under treatment with aspirations and irrigations it is supposed to be due to the underlying lung disease and this has to be treated; thoracoplasty should be done, if the other lung is not affected and if the general condition of the patient is good. In mixed infection empyema immediate surgical drainage by thoracotomy is indicated. As soon as the patient's condition permits, thoracoplasty should be performed.—*Traitements des pleurésies purulentes chroniques*, J. P. Roger & J. M. Lemieux, *Laval méd.*, February, 1944, 9: 70.—(G. C. Leiner)

**Outlining of Empyemal Walls.**—By spraying only 10 cc. of 35 per cent diotrast solution into open empyemal spaces, the pleural walls are clearly outlined in the X-rays. The method of course cannot be used for noncommunicating or incompletely drained loculations inaccessible to the spray. (Skiodan in acacia solution has also been used but must be kept warm to prevent plugging in the atomizer.) To remove the loose coagulum (which takes up the contrast medium and obscures results) the empyemal space should be thoroughly irrigated with saline or azochloramide solution. The patient then lies with



affected side uppermost and the spray is used, care being taken not to obstruct the exit, to allow free egress of air, to avoid pressure within the chest cavity. The patient is then tilted toward the side of the wound and excess fluid is drained off. Hard X-ray films (postero-anterior and lateral) are taken immediately. As the contrast medium is rapidly absorbed it does not cause confusion in subsequent X-rays. The method is inexpensive and effective.—*Roentgenographic Demonstration by Diotrast of the Pleural Walls in Open Empyema*, J. Gordan, *J. Thoracic Surg.*, April, 1944, 13: 162.—(W. M. G. Jones)

**Mediastinal Pleurisy in Infants.**—Pleurisy involving the anterior portion of the superior mediastinum produces a roentgen picture similar to but differing from that produced by an enlarged thymus. Other conditions with which mediastinal pleurisy may be confused are partial atelectasis of the lung, pneumonic infiltration, stasis in the superior vena cava by pressure from an elevated bronchus, enlarged hilar nodes, infections of the thymus gland, tumors of the thymus gland, dilated left auricle, retrocardinal aneurysm, paravertebral abscess, spondylitis deformans, oesophageal diverticulum, dilated oesophagus, scoliosis, pericardial fat tab, ganglioneuroma of the vagus nerve, and tumor of the pericardium. A case of unilateral thymus gland enlargement is described for comparison with 8 cases of mediastinal pleurisy in patients under one year of age. Although only one of the cases was autopsied, they all closely resemble proved cases presented by other authors. Clinically there is no single symptom or group of symptoms that would permit a definite diagnosis of mediastinal pleurisy even with effusion, without roentgen examination of the chest. Cough is the most common symptom, occurring in 6 of the author's 8 cases. Usually the cases are pneumonic in origin, frequently showing recurrences of pneumonic infection, and some cases being more specifically designated as "pleuropneumonia." Physical findings are usually related to the pneumonia rather than to the pleurisy or effusion. In

only one case was widening of the mediastinum detected by percussion prior to roentgen examination. The course is relatively benign as evidenced by the low mortality. Two deaths in the series were related to complicating factors (heart disease and mongolian idiocy). Treatment has been symptomatic except for the pneumonic recurrences which were treated with sulfonamides. Diagnostic or therapeutic aspiration of fluid was not attempted. Roentgen therapy directed to the anterior mediastinum in 2 cases did not shorten the course of the process. Of all the infections involving the anterior mediastinal nodes, tuberculosis is apparently rare. Roentgen recognition of this form of pleurisy is important but the criteria which are used to distinguish it from unilateral thymus gland enlargement are not generally known. This form of mediastinal pleurisy, with or without effusion, is characterized by: (1) a sharp lateral margin; (2) termination in an inferior angle of less than 90 degrees and in relation with or near the interlobar fissure; (3) greater frequency of unilateral involvement, more often on the right side; (4) frequent inflammatory changes in the adjacent lung parenchyma; (5) increase in the width and density of the interlobar fissure shadow; (6) occurrence of greatest density inferiorly in the lateral projection; (7) occurrence of the density anywhere between the anterior and posterior boundaries of the pleural space in the lateral projection; (8) absence of tracheal deviation or distortion in the lateral projections (persistent lateral deviation to the affected side in the postero-anterior view occurred in 2 cases); (9) minimal changes in the size and contour of the density during quiet or labored respiration; (10) no significant reduction in size after small doses of roentgen therapy. In contrast to the preceding criteria, significant thymus gland enlargement is characterized by: (1) a larger shadow which overlaps part of the cardiac shadow; (2) rounded corners, usually 90 degrees or more; (3) considerable change in contour with respiration and crying; (4) bilateral mediastinal enlargement, although asymmetries and un-

ilateral forms are well known; (5) variable degrees of tracheal and oesophageal deviation or compression in one or both planes (this point is still widely disputed in the literature); (6) occurrence of the density anteriorly and superiorly in lateral projections; (7) decrease in size after small doses of roentgen therapy. It is possible to have both pleurisy and thymus gland enlargement simultaneously. Improvement in symptoms following a roentgen treatment without much reduction in the angular shadow is possible in that thymus tissue present and obscured by the pleural density could be reduced so as to allow shift or redistribution of any fluid present. Occasional reports of roentgen resistant thymus glands should be checked for possible misinterpretation of the findings. The greatest source of error arises from poor positioning or alignment in roentgenography. Slight rotation of the patient may completely obscure portions of the mediastinal border. Low positioning of the tube accentuates these angular deformities and in 2 of these cases the residual thickened pleura cast a solid triangular shadow from this angle. Correct alignment in these same cases showed only linear shadows representing thickened pleura in the central interlobar fissure area. This thickening was a residual characteristic of all the cases which cleared of their major density during the period of observation.—*Mediastinal Pleurisy in Infants*, R. A. Harvey, *Am. J. Roentgenol.*, February, 1943, 49: 145.—(W. H. Merritt)

**Widened Mediastinum in Children.**—The authors found that a number of infants and children were hospitalized for periods as long as one to three years solely because of roentgenographic evidences of "widened mediastinum" or "enlarged" mediastinal and tracheobronchial lymph nodes. During this period the children had been roentgenographed in the horizontal position, a practice which is still prevalent in most institutions. Since the institution of upright chest roentgenography, a considerable number of children have been discharged because of the sudden restitu-

tion of the mediastinal shadow to the normal. This change occurred solely because of improved technique of roentgen examination. The difference in results with upright and horizontal chest roentgenography was compared and analyzed in 25 cases. Ten of these cases were selected for special study to determine the effects of phase of respiration, position (upright or horizontal) and type of projection (anteroposterior and postero-anterior). It was almost invariably found that the roentgenograms made in the postero-anterior upright position at the end of inspiration were the most satisfactory and gave the least distorted and least misleading views of the heart and mediastinum. If, in addition, a method of synchronizing the exposure with the same phase of the cardiac cycle is employed, successive roentgenograms on different days are absolutely comparable, particularly in regard to heart size and shape. Changes in the size and appearance of the mediastinal and heart shadows on the roentgenogram may be produced by various factors among which the most important are position (whether horizontal or upright), effect of gravity, phase of respiration and phase of the cardiac cycle. The changes so produced are important, since serious mistakes in diagnosis such as hypertrophied thymus, childhood tuberculosis, congenital or acquired valvular heart disease and bronchopneumonia have been made in normal cases. These mistakes are easily made unless one understands the effect of the various factors producing the alteration in the roentgenogram. Great variation in the size of the mediastinum has long been recognized and ascribed to change in position. In the cadaver, Cunningham states that, owing to the weight of the heart, the anterior mediastinum is increased and the posterior mediastinum is reduced in the anteroposterior depth. From this it can be inferred that the mediastinal structures can move in anteroposterior direction because of available space and force of gravity. In the supine position the mediastinal structures tend to drop posteriorly. Because of the vertebrae there is no yielding space posteriorly

and, as a result, the structures spread laterally, pushing the lungs before them. The amount of lateral displacement is appreciable as the roentgenograms demonstrate. In the prone position, the mediastinum structures move anteriorly. Again, the mediastinal structures tend to spread laterally, but owing to the soft compressible fibro-alveolar tissue and the space in the anterior mediastinum it more nearly approaches the sternum and the lateral displacement is minimal. Thus it may be stated that in the horizontal position, the postero-anterior (prone) view will produce a narrower mediastinal shadow than the antero-posterior (supine) view. This is also due to another important factor which holds true for both the horizontal and upright positions, namely that the trachea, lymph nodes, heart and vessels all lie closer to the anterior surface of the body than the posterior. Another important rôle in increasing the width of the mediastinal shadow in the horizontal position can be ascribed to the abdominal organs. These tend to push up the diaphragm, thus shortening the vertical diameter of the thorax and causing lateral expansion of the mediastinal structures. Again, in the horizontal position widening is added to by distention of the superior vena cava and innominate vein on the right and the subclavian vessels on the left. In the upright position, the blood vessels empty, the abdominal viscera drop and the mediastinum tends to recede inferiorly. In doing so, the lateral displacement is minimized and the mediastinal shadow is correspondingly narrowed. Groedel and Dietlen believe that narrowing of the mediastinum during inspiration and widening during expiration are due to the changing position of the diaphragm. Dietlen admits a widening in early inspiration due to sudden filling of superior vena cava and right auricle as the result of suction effect. The crying effort also influences the size of the heart and mediastinum. During the forced expiration incidental to the crying effort (Valsalva effect) the narrowed glottic chink offers a decided resistance to the column of air. As a result the intrapulmonary pressure is raised and the heart swings on

its long axis, the apex coming forward and the base backward. Its narrower diameter is therefore presented; the projected area is lessened for the greater part of this phase and is only broad for a moment, at the extreme end of expiration. Thus in the crying child the transverse cardiac diameter is less than at inspiration, even though the chest has narrowed and the diaphragm has risen. Marked changes in the size of the heart are due to changes in the phase of the cardiac cycle. The size and shape of the heart should be judged only in comparison with previous or subsequent teleroentgenograms made in the upright postero-anterior position, in inspiration, and using short exposures (one-tenth second or less). If, in addition, means are available to synchronize the exposure with a particular phase of the cardiac cycle, the likelihood of error is reduced to a minimum. The writers agree with Pancoast that "unless there are clinical evidences and lateral X-rays of the neck to show definite buckling of the trachea, it is impossible to make a diagnosis of enlarged thymus." To this can be added that no such diagnosis should be based solely on horizontal roentgenograms. A simple inexpensive device can be made to provide upright chest roentgenograms; the authors describe one of their own.—*Study of the "Widened" Mediastinum in Children and Pitfalls in Diagnosis*, A. V. Shapiro & L. Bell, *Am. J. Roentgenol.*, February, 1943, 49: 159.—(W. H. Meritt)

**Diaphragmatic Hernia.**—There are two main forms of diaphragmatic hernia: non-traumatic and traumatic. The congenital variety of nontraumatic hernia is attributable to embryologic deficiency and usually does not have a hernial sac. The more common sites of a congenital hernia present at birth in the probable order of frequency of occurrence are: (1) through the pleuroperitoneal hiatus (foramen of Bochdalek); (2) through the oesophageal hiatus; (3) through an anterior substernal opening (foramen of Morgagni or Larrey's spaces); and (4) through the gap left by partial absence of the diaphragm, a gap which is usually situated in

the posterior part of the muscle. If the hernia is acquired after birth, the sites of occurrence are: (1) through the oesophageal hiatus (this type has a hernial sac); (2) through the region of fusion of the anlage of the diaphragm; and (3) at sites named under the congenital type. Traumatic hernia may be caused by direct or indirect injury, or by inflammatory necrosis of the diaphragm. Of 295 cases in which surgical treatment was employed, the most common types were oesophageal hiatus hernia, pleuroperitoneal hiatus hernia, hernia attributable to congenital absence of the posterior portion of the diaphragm, subcostosternal hernia and traumatic hernias caused by direct or indirect injury and those caused by inflammatory necrosis. Oesophageal hiatus hernia, the most common variety in adults, is a sliding herniation of the stomach into the posterior mediastinum. The hernia may progress until the entire stomach is contained within the hernial sac; the colon, omentum, and occasionally the spleen also may be drawn into the sac. True oesophageal hiatus hernias can be classed into two types: In the first type the oesophagus is of normal length and its lower end is not elevated above the diaphragm, but a portion of the stomach has herniated into the posterior mediastinum, beside the oesophagus. This type of hernia is often designated as para-oesophageal hiatus hernia. The hernias are usually small to moderate in size and rarely involve more than a fourth to a half of the cardiac end of the stomach. About a third of the oesophageal hernias were of this type. In the second type of oesophageal hiatus hernia, the oesophagus is of normal length but its lower end is elevated above the diaphragm, and the herniated stomach is in the posterior mediastinum. The size of the hernias is usually larger than that of the first type. From a third of the stomach to the whole stomach, a portion of the omentum and occasionally a portion of the colon are within the hernial sac. These hernias usually fill the entire mediastinum and generally project into the left side of the thoracic cavity but may project into the right side or both sides. Hernias of this type constitute

two-thirds operated upon by the writer. Hernias of the first type may ultimately develop into those of the second type as more of the stomach is included in the hernial sac. In many cases the lower end of the oesophagus is dilated. Two additional types of oesophageal hiatus hernia, which may be considered pulsion varieties, have also been recognized. These hernias are probably attributable to atrophy of the elastic fibres of the diaphragmatico-oesophageal membrane together with relaxation of the circular muscle surrounding the oesophageal opening, with a resultant incompetent hiatus. The establishment of the diagnosis usually requires both oesophagoscopy and roentgenography. One type closely simulates the para-oesophageal type of hernia, except that it is relatively small. A definite hernial sac is beginning to form. The oesophagus is only slightly elevated; the abdominal portion is elevated to the superior border of the diaphragm. The hernia may remain small or develop into a true para-oesophageal hernia. In the other type, the entire hiatus is incompetent, the cardiac end of the stomach protrudes above the diaphragm and there is comparable elevation of the oesophagus. This type does not have a true hernial sac and may not be considered a true hernia. Oesophagoscopy shows the length of the stomach to be normal, differentiating it from a congenital short oesophagus. Congenital short oesophagus with partial thoracic stomach is not a true hernia because the shortness of the oesophagus has kept the stomach suspended above the diaphragm. This condition is relatively rarely found at operation. The condition of short oesophagus includes that in which the oesophagus is congenitally short and that in which ulceration and occasionally malignant neoplasm is followed by cicatricial contraction of the lower end of the oesophagus and drawing of the gastric cardia above the diaphragm. Dilatation of the lower end of the oesophagus with relaxation of the cardia of the stomach simulates oesophageal hiatus hernia of the pulsion type. Oesophagoscopic biopsy of the mucosa at the site of the dilatation is necessary to establish the diagnosis.

The position of the left kidney may be helpful in distinguishing between the pleuroperitoneal hiatus (Bochdalek foramen) type of hernia and that resulting from the absence of the posterior portion of the diaphragm; in the former, the kidney is in the normal position; in the latter it is usually above the normal diaphragm in the lower part of the thorax. These hernias do not have a hernial sac; they produce marked or complete collapse of the left lung and often marked shift of the mediastinum to the right. Operation should be performed for these congenital types of hernia as soon after birth as the condition is recognized. The subcostosternal type (foramen of Morgagni) of hernia is usually unilateral and on the right side. When the colon is herniated, the roentgenological diagnosis is readily established. When the omentum is the only abdominal structure in the hernia, the appearance may simulate neoplasm. In some instances an elevated position of the colon may be suggestive. The traumatic type of hernia occurs most frequently on the left side, usually in the posterolateral portion and dome of the diaphragmatic muscle. Hernias due to inflammatory necrosis of the diaphragm, following rupture of a subphrenic abscess on the left side, are included in the traumatic variety. There is no hernial sac. Roentgenograms of the chest are made and read immediately after all operations. Mediastinal displacement due to pneumothorax is corrected by withdrawal of sufficient air. Pulmonary congestion due to retained or aspirated secretions is best relieved by immediate bronchoscopic aspiration of the lung. In the series of 295 operated cases there were 12 deaths, a mortality of 4 per cent.—*Roentgenologic Considerations of the Diagnosis and Treatment of Diaphragmatic Hernia*, S. W. Harrington, *Am. J. Roentgenol.*, February, 1943, 49: 185. —(W. H. Merrit)

**Signal Node in Cancer.**—The deep inferior cervical nodes are of special importance in the subject of metastatic cancer. These nodes may be primarily involved by cancer of the head and neck, but the relative frequency of involvement in thoracic and intraabdominal

cancers has directed early attention to their special position, notably Virchow's and Troisier's. They are closely associated with the important lymphatic collecting channels, the great lymphatic vein on the right, and the thoracic duct on the left. The nodes are connected to the channels by the efferent lymphatics, and ordinarily the flow of lymph is from the node into the ducts. Under pathological conditions the flow may become reversed and cancerous invasion follows. Lymphatic metastasis to distant organs may occur by way of emboli or by direct propagation through the lymph channels. In either case the orifice of the duct near the jugular vein becomes occluded, and the direction of the lymph current is reversed. The invasion of the supraclavicular nodes from abdominal or thoracic cancers is, therefore, always retrograde. The "sentinel" node is invaded most frequently by thoracic cancers, but during the course of their evolution many abdominal cancers metastasize there. The finding of such metastasis generally denotes a poor prognosis although it is possible to prolong life by eradication of the primary cancer and radiation to the metastatic nodes. Frequently the presence of a hard tumor mass in this location is the first indication of malignancy somewhere in the body, and only prolonged diagnostic search leads to the discovery of the primary source. At other times the primary location is demonstrated at autopsy only. In the majority of patients the signal node is invaded only in the advanced stages of the disease. Among 4,365 patients studied, 122, or 2.8 per cent, presented metastasis to the signal node in thoracic or abdominal cancers. In 41 of these it was the first sign of malignancy. In primary carcinoma of the lung the signal node was involved in 13.2 per cent of the cases. Next in order of frequency, carcinoma of the pancreas involved the node in 8.1 per cent, oesophagus 7.1 per cent, ovary 6.1 per cent, testis 4.8 per cent. Although involvement of the node in carcinoma of the stomach is found only in 2.6 per cent, this was a frequent cause because of the high incidence of this type of carcinoma. Intraabdominal carcinomata usually metas-

tasize to the left node, whereas thoracic tumors affect both sides almost equally.—*Significance of Supraclavicular Signal Node in Patients with Abdominal and Thoracic Cancer*, E. Viacava & G. Pack, *Arch. Surg.*, February, 1944, 48: 109.—(H. Marcus)

**Solitary Lung Tumors.**—During the past ten years, 23 patients with a solitary circumscribed opacity in the lung measuring at least 2 inches in diameter were seen. The most common symptoms were weight loss (in 12 patients), cough (in 10), chest pain (in 10). Six patients had no obvious complaints; physical findings were absent in about half of the patients. The final diagnoses were: primary malignant tumors in 14 cases, metastatic malignant tumors in 3 cases, benign lung tumor in one case, tuberculomata (with negative sputa on cultures) in 4 cases, chronic lung abscess in one case. Bronchoscopy, which was done in 14 patients, gave a positive biopsy in only two. Four patients were diagnosed on the basis of clinical characteristics. In 7 patients the diagnosis was made at autopsy. Exploratory thoracotomy, which is recommended as an early diagnostic aid, led to the diagnosis in 10 cases.—*Solitary Circumscribed Tumors of the Lung*, T. F. Thornton, Jr., W. E. Adams & R. C. Bloch, *Surg., Gynec. & Obst.*, April, 1944, 78: 364.—(G. C. Leiner)

**Pulmonary Mucous Epithelial Hyperplasia.**—Two cases of this condition are described. In both, the disease picture was somewhat obscured by severe superimposed bacterial infections. On X-ray films the first case showed many homogeneous shadows on both sides, more pronounced at the bases, interpreted as a possible fungus infection or a tumor. Severe dyspnoea preceded death. The patient, a male, was sixty-two years old. The lungs showed the only pathological changes of note. These consisted of a dilatation of the alveoli and a covering of the alveolar walls by a simple columnar epithelium. In a few cases this epithelium showed a transition to a cuboidal type, but as a rule the change from the abnormal epi-

thelium to the usual type was abrupt, as if the alveoli were being invaded by the pathological cells. In some areas the columnar epithelium had formed small papillary processes. The columnar cells were not ciliated and no mitoses were noted. No abnormal cells were found in the lymphatic tissues of the lungs. The bronchiolar epithelium, and that of the alveolar ducts, did not seem to be affected by this process. The second case was that of a white female, seventy-nine years of age, who had long suffered from what was diagnosed as primary anaemia. The patient died with symptoms of pneumonia. On necropsy the lung sections showed certain microscopical changes which were of interest. Although most sections showed merely a confluent bronchopneumonia, in the left lower lobe, in the lingula of the left upper lobe, and in a small portion of the right upper lobe, a condition was found similar to that observed in case one, except that the columnar epithelial cells were proportionately higher so that they almost obliterated the lumen of the alveoli in some areas. The left lower lobe had been almost completely replaced by hyalinized collagenous fibrous tissue but it contained islands of abnormal epithelial lining. The bronchi and bronchioles, as in case one, were unaffected. The pathological findings in these two cases have much in common with those rare tumors (pulmonary adenomatosis) described by Helly, Bonne and others. As a similar condition, recognized as a virus disease, is known to occur in sheep (jaagsiekte) the authors consider the possibility of a viral aetiology in this disease. This condition, however, is of little significance in a consideration of the genesis of pulmonary carcinoma in general. (With 4 plates.)—*Pulmonary Mucous Epithelial Hyperplasia (Pulmonary Adenomatosis): A Report of Two Cases*, E. B. Taft & D. A. Nickerson, *Am. J. Path.*, March, 1944, 20: 395.—(J. S. Woolley)

**Hyperplasia of Pulmonary Alveolar Epithelium.**—In the early part of fetal life the lung has a glandular appearance and the alveoli are lined by a continuous epithelial layer. But in the latter part of the intra-

uterine period the capillary bed develops extensively, and numerous capillaries break through the epithelial lining, leaving the epithelium as isolated round cells. In the postnatal lung the alveolar walls are formed almost entirely by the capillaries, but a few epithelial cells persist in the niches between the capillaries. In any disease which brings about marked thickening of the interalveolar septa, with displacement of the capillaries away from the surface and consequent loss of respiratory function, the alveolar epithelium may undergo hyperplasia to form a continuous epithelial lining. The cells are either cubical or columnar and some of them may secrete mucin. There is convincing evidence that the epithelium forms locally and does not grow in from the bronchi. In chronic passive congestion and in interstitial pneumonia, epithelialization of the alveoli follows thickening of the interalveolar septa. Mild irritation of the alveolar walls from foreign bodies may also bring about epithelialization, as in lipoid pneumonia. In *jaagsiekte* of sheep widespread epithelialization of the alveoli occurs. *Jaagsiekte* is a serious endemic infectious disease in sheep prevalent in South Africa. A similar disease in sheep in Iceland has been described. The aetiology of this disease is unknown but the microscopical features suggest direct irritation of the cells by a virus which attacks them. In 1939 Bonne described a case of diffuse epithelialization of the pulmonary alveoli in a thirty year old Chinese male. This case strikingly resembled *jaagsiekte* in sheep. A similar case is reported by the present author. The patient, a sixty-three year old male, complained of dyspnoea on exertion, a productive cough, weakness and loss of weight. On introduction of lipiodol the small bronchi showed unusual narrowing. The tentative clinical diagnosis was carcinoma of the lung. Death ensued a few months later and microscopical examination of the lungs showed every alveolus lined by cubical or columnar epithelium, much as in the case reported by Bonne. The septa were not destroyed by epithelial invasion as one would expect if the growth were carcinoma.

The lesion was not an interstitial pneumonia and the epithelialization was not found due to thickening of the septa or to foreign material in the alveoli. Human pulmonary tumors reported as multiple adenoma or carcinoma have a microscopical structure similar to this case and the case of Bonne. The alveoli are lined by epithelial cells and the interalveolar septa are intact. In a few instances metastases have been found. There is no good reason to doubt that hyperplasia of the alveolar epithelium may give rise to localized or diffuse adenomatous growths which may form metastases. (With 2 plates.)—*Hyperplasia of the Pulmonary Alveolar Epithelium in Disease*, E. T. Bell, *Am. J. Path.*, November, 1943, 19: 901.—(J. S. Woolley)

**Mediastinal Ganglioneuroma.**—These comparatively rare neurogenic tumors arise in the posterior mediastinum. It is important to diagnose them correctly as their prognosis is good. The cure lies in surgical removal. The approach is posterior. If the tumor is small, an intercostal incision is sufficient. Otherwise parts of one or two ribs may be excised. At times incomplete removal is all that can be accomplished because of adherence of the tumor to surrounding structures, especially the vertebral spine. Even so, recurrence need not be feared. The history usually is of long duration. Symptoms are due to pressure of the tumor on surrounding structures, notably the trachea and bronchi, the inferior laryngeal nerve, or the superior cervical sympathetic ganglion. The tumor may be small and symptomless, and in such cases it is usually discovered on routine X-ray examination. Any patient with a posterior mediastinal tumor who appears to be in good condition should be suspected of a ganglioneuroma. Pathologically, the tumor is well encapsulated, and it contains fibrous tissue with nerve elements, such as ganglion cells and satellite cells. At operation the entire sympathetic chain should be examined carefully since multiple tumors are occasionally found. —*Mediastinal Ganglioneuroma*, H. K. Gray, D. V. Shepard & M. B. Dockerty, *Arch. Surg.*, March, 1944, 48: 208.—(H. Marcus)

**Aspiration Biopsy of Intrathoracic Neuroblastoma.**—This is a case report of a five-month-old infant who offered a puzzling symptomatology and was finally diagnosed by aspiration biopsy under fluoroscopic guidance. At the age of three months, the child developed hyperpyrexia, restlessness and profuse perspiration. At the time of hospitalization he was dyspnoeic and pallid, the liver was enlarged and the abdomen distended. Flatness and suppressed breath sounds were present over the right lower lobe. X-ray revealed a sharply circumscribed rounded density, 6 cm. in diameter, at the right base posteriorly; subcutaneous diodrast films showed what was thought to be a soft tissue mass at the superior pole of the right kidney. Biopsy specimen under fluoroscopic control suggested tumor and a tentative diagnosis of neurocytoma of the adrenal was made; the thoracic mass, it was believed, was due to extension upward—either directly or by liver metastasis. Operation by abdominal approach showed the mass to be entirely supradiaphragmatic. The pleural cavity was therefore entered and the mass removed, leaving some tumor tissue behind with the pedicle, which was attached to the bodies of the lower dorsal vertebrae. The patient succumbed three and one-half hours post-operatively. At autopsy the abdomen was normal, except for an enlarged liver. The right lung was collapsed and the right retropleural ganglion chain involved. The pathological diagnosis of the tumor was neurocytoma (atypical). Neuroblastomata occur wherever sympathetic nervous tissue is present; the usual site is the abdomen. Of the retropleural tumors, a dense rounded shadow in the posterior portion of the chest is of diagnostic importance. Since the symptomatology depends upon signs of pressure or metastasis, which may be absent, and since intrathoracic involvement may be mistaken for other types of pulmonary lesions, aspiration biopsy under fluoroscopic guidance would seem to be a logical procedure in some cases.—*Intrathoracic Neuroblastoma*, W. E. Lee & J. A. Ritter, *Ann. Surg.*, June, 1943, 117: 93.—(D. J. Rednor)

**Endothelioma of Pleura.**—Primitive endotheliomata of the pleura are rare tumors. Among 10,000 tumors of all types only one is seen. The first sign of the presence of the tumor is a pleural effusion. On aspiration this contains varying amounts of blood, usually microscopical amounts at first, but it later may become hemorrhagic. Examination of the fluid shows typical tumor cells. The cells are frequently multinucleated, with dark nuclei, and show many mitoses. The underlying lung is atelectatic. People in middle age are usually affected, without a sex preference. The case reported in this communication showed symptoms for sixteen months prior to death. The outstanding complaint was dyspnoea. The effusion was massive and tended to accumulate rapidly after removal. In all, 66 liters of fluid were removed during the course of the illness. Although autopsy was not performed, the tumor was easily demonstrated by thoracoscopy. It was diffusely distributed over the pleura. Healthy pleura alternated with necrotic patches, and in other areas the tumor was present as papillomatous or solid structures. Whether this tumor arises from the pleural endothelium as such or from the blood vessels or lymph channels within the pleura remains undecided.—*Un cas d'endothéliome primitif de la plèvre*, J. Stephani & A. Besse, *Schweiz. med. Wchnschr.*, December 31, 1943, 73: 1580.—(H. Marcus)

**Mediastinal Lymphosarcoma.**—A thirty-nine year old woman developed chest pain, cough and loss of weight in 1930. In 1932, when the complaints had become worse and anorexia, difficulty in swallowing and swelling in the right side of the neck had appeared, the physical examination showed masses of firm lymph nodes on both sides of the neck; the roentgenological examination of the chest revealed a large well defined, rounded, homogeneous shadow filling the upper two-thirds of the right lung field with its base in the mediastinum. The diagnosis of mediastinal neoplasm was made. Deep roentgen therapy was administered, which was followed by regression of the tumor masses. The treatment



was repeated several times during the following years. Because of attacks of dyspnoea the patient was admitted to Morissania Hospital in 1942. X-ray examination showed a large, irregular, oval calcified mass to the right of the heart. An operation was performed and a large, lobulated, hard mass was found behind the heart. The mass was densely adherent and could not be removed. The patient died soon after the operation. The clinical course and the marked regression of the neoplasm under roentgen therapy are supposed to be strongly indicative of a malignant lymphosarcoma.—*Mediastinal Lymphosarcoma: Report of a Case under Roentgen Therapy for More than Ten Years*, E. B. Bilchick & A. W. Jacobs, *New York State J. Med.*, April 1, 1944, 44: 731.—(G. C. Leiner)

**Mediastinal Dermoid.**—To date, 229 cases of mediastinal dermoids and teratomata have been published. The tumors are classified as simple dermoid cysts, complex dermoid cysts and teratomata. Simple cysts are lined with epithelium and their wall contains hair follicles, sweat and sebaceous glands. They are filled with thick sebaceous material. Complex dermoid cysts contain the same type of material, but there are outpouchings from the cyst wall into the lumen which are lined by epithelium. In the depth of these, mesodermal elements, such as bone, cartilage, smooth and striated muscle, are found. Teratomata have elements of all three germ layers. They are classified as adult or embryonal. The latter type is prone to degeneration into malignant tumors which show a mixed sarcomatous and cancerous character. If the tumors are not malignant, they produce their symptoms by pressure on the important thoracic structures, interfering with respiration and circulation. Radical surgical removal is the only rational therapy. The origin of these tumors is in doubt. The theory that they represent a homologous twin which was taken up into the body of its twin at an early age has been abandoned. The chief argument against this theory is that even the most highly dif-

ferentiated teratomata fail to show a metameric arrangement as is the case with the most primitive examples of malformed twins. The more modern conception is that teratomata originate from the omnipotent tissue of the blastopore and as the embryo develops are included in it. Whether the same theory applies to dermoids is not known at this time. A case of mediastinal dermoid is presented in this article. The large tumor collapsed the right lung and was so firmly adherent to the right heart from base to apex that no pericardium could be made out grossly. The wall of the tumor, on microscopical examination, fused with the pericardium and with the myocardium. The latter showed inflammatory and degenerative changes underlying the tumor. In this case, as in 2 other cases reported in the literature, the question arises whether the tumor secondarily became fused with the pericardium through inflammatory changes, or whether it originated in the pericardium.—*Mediastinal dermoid*, A. Zingg, *Schweiz. med. Wchnschr.*, November 27, 1943, 73: 1440.—(H. Marcus)

**Hodgkin's Disease.**—The authors classify Hodgkin's disease into three types—para-granuloma, granuloma and sarcoma. The paragranuloma type is the most benign form both histologically and clinically. In almost all cases this type of Hodgkin's disease begins in the cervical lymph nodes and its behavior suggests an infectious process rather than a true tumor. The granulomatous form of the disease also suggests an inflammatory origin whereas the sarcomatous type has all the characteristics of a true neoplasm. In the authors' conception of disease, the paragranulomatous and granulomatous forms have a common aetiology, the latter representing a more virulent exciting agent or a less immune host. Bacteriological studies of excised lymph nodes taken from persons sick with Hodgkin's disease failed to yield positive significant results and the authors are forced to conclude that the aetiology of this disease has yet to be discovered. Investigation further indicated that Hodgkin's granuloma ac-

counts for approximately 0.25 per cent of deaths in a general hospital. The paraganulomatous and granulomatous forms occur at all ages, although they appear to be more uncommon in infancy and in extreme old age, and are more common in males than in females (70:30). The sarcomatous form differs in that it occurs chiefly in the middle-aged or elderly, 80 per cent occurring over the age of forty in the authors' series of 51 cases, and the sex distribution was equal. A patient may begin with the more benign paraganulomatous type and with time the disease may be transformed to the granulomatous and later sarcomatous types but never the reverse.—*Hodgkin's Disease*, H. Jackson & F. Parker, Jr., *New England J. Med.*, January 6, 1944, 230: 81.—(J. Ballinger)

**Osteomyelitis of Thoracic Spine.**—The authors present a case of pyogenic osteomyelitis of the thoracic spine presenting as a case of primary pulmonary disease. From the onset throughout seven months of hospitalization the clinical findings suggested a tentative diagnosis of inflammatory disease of the lungs. The constant manifestations were pain in the chest, profuse expectoration, frequent and severe haemoptysis, dyspnoea and sepsis. Roentgenographic examination supported such an opinion since vertebral abnormalities were not seen until late in the course. The early roentgenographic changes were related only to the pulmonary lesions; a diffuse density was present in the lower part of the left upper lobe; evidence of mediastinitis was not noted. Because of the profuse purulent expectoration, haemoptysis and suggestive roentgen findings, bronchiectasis could be inferred. In the absence of other causes, the possibility of an infected bronchial ectasia resulting from a previously expelled foreign body necessitated consideration. Bronchography and repeated bronchoscopies were therefore performed. Tuberculosis and other specific infections of the lung or bronchus were excluded by roentgen examinations, bronchoscopic and sputum studies. Evidence for abscess or necrosis of the lung was likewise lacking. Mediastinitis

on the right side became definitely apparent on the chest roentgenograms five months after onset of illness. However, because of the extensive opacity in the left lung field it was not considered likely that all of the chest involvement could arise from a vertebral osteomyelitis. Such a view was apparently supported when roentgenograms of the dorsal spine made at about the same time were described as showing no evidence of disease. As the mediastinal abscess enlarged the nodular outline of the widened root shadow grew large, lost its sharp delineation from the surrounding lung tissue and suggested the diagnosis of mediastinal lymphoma. The presence of a palpable spleen appeared to confirm this diagnosis, and the destructive vertebral changes which appeared were ascribed to bony extension of the lymphoma. Deep roentgen therapy of the abscess which was mistaken for lymphoma was soon followed by pointing of the mediastinal suppuration with paravertebral abscess formation and accentuation of the septic state. Bilateral brachial plexus nerve root signs due to pressure associated with the diseased vertebrae, and indicated by weakness of the arms and atrophy of the small muscles of the hand, developed late. However, a noteworthy manifestation of vertebral involvement which was present from the onset was the fixed, supine position which the patient constantly assumed. Roentgen evidence of osteomyelitis with destruction of the dorsal vertebrae finally became apparent seven months after the onset of symptoms, concomitantly with the superficial pointing of the abscess. By this time the vertebrae were completely riddled with the pyogenic infection and the disease had become far advanced. At autopsy the destruction of the dorsal vertebrae by pyogenic osteomyelitis was very extensive, and the other changes were essentially those of suppurative mediastinitis. No gross bleeding areas in the bronchi were found to explain the severe and frequent haemoptyses which were apparently due to congestive changes.—*Pyogenic Osteomyelitis of the Thoracic Spine Presenting as Primary Pulmonary Disease*,

H. A. Solomon & A. L. Bachman, *Am. J. Roentgenol.*, February, 1943, 49: 219.—(W. H. Merrit)

**Lupus Erythematosus Tumidus.**—Tumor forms of lupus erythematosus are rare variants of the discoid type. They may be located either superficially or deep, the former in the cutis and the latter in the subcutis. There is both direct and circumstantial evidence of the tuberculous origin of these tumors. If lupus erythematosus of the discoid type itself may result from a tuberculous infection, there is no reason why its variant may not develop on the same aetiological basis. Furthermore, a case of lupus erythematosus tumidus has been reported in the literature whose suspected tuberculous origin was confirmed by guinea pig inoculation. In the author's case of this skin disease the lesion remained unchecked for three years. Yet, one week after the first intracutaneous injection of tuberculin, retrogressive changes were obvious. Furthermore, the display of a high allergy to tuberculin, repeated focal reactions following excessive dosage and the unquestioned favorable therapeutic response were further indications of the tuberculous nature of the disease. In the present case prolonged intracutaneous tuberculin therapy proved efficacious. About 10 per cent of the original tumor remained after fourteen and one-half months' treatment. (Illustrated.)—*Lupus Erythematosus Tumidus Superficialis, Treatment with Tuberculin: Report of a Case*, S. Irgang, *Arch. Dermat. & Syph.*, July, 1943, 48: 60.—(J. S. Woolley)

**Amyloidosis and Major Surgery.**—Recovery from amyloidosis is said to be rare, and the disease usually progressive and fatal. In the case reported here four stages of thoracoplasty were done for a large chronic empyema, and seven months later an extensive Schede thoracoplasty was necessary to obliterate the residual paravertebral sinus which extended from the eighth rib to the apex. The patient stood his surgery extremely well and is working today, four years later. At

onset, two years before surgery, the amyloidosis was quite extreme, the liver edge at the iliac crest, urine specific gravity 1005 to 1010, albumin 4 plus, non-protein nitrogen 30 to 40 mg. per cent, congo red retention 80 to 97 per cent, and blood red cells 2,200,000. The patient suffered greatly from persistent nausea and vomiting, body wasting, haemorrhages from mucous membranes and chest wound. He was kept alive with intravenous fluids and transfusions, high vitamin, high protein diet with liver and iron added. After a year the liver had reduced in size but at time of surgery was still at the umbilicus level. Other tests changed little though the anaemia improved and weight increased. His endurance and recovery under surgery are considered remarkable.—*Major Surgery in Amyloidosis*, J. M. Beardsley, *J. Thoracic Surg.*, August, 1943, 12: 590.—(W. M. G. Jones)

**Pulmonary Oedema.**—Oedema of the lungs is a common sequel of exposure to irritant gases both in civilian and in military life. In poisoning with gases that are very water soluble the damage may be confined to the upper respiratory tract. The gases that are relatively insoluble in water exert their chief effect on the lungs. The result is thrombosis of pulmonary blood vessels, concentration of blood in the pulmonary capillaries, outpouring of blood and serum into the alveoli, followed by bronchopneumonia and death, or by bronchiectasis and multiple abscess formation. Symptoms of gas poisoning may become apparent immediately after exposure or may be delayed for as long as twelve hours. The usual treatment of warmth and breathing of oxygen enriched air mixtures is helpful in some cases, but it frequently does not prevent the onset of pulmonary oedema, nor does it abolish it once it has developed. Anoxia is the usual result of the inhalation of irritant gases. It is due to swelling of the alveolar cells which prevents the usual absorption of oxygen, to the narrowing of bronchial pathways due to spasm of injury, and to the presence of serum, blood, and mucus in the alveoli. The bronchiolar spasm

causes an increased respiratory effort which in turn causes an increasingly negative intrapulmonary pressure. This exerts a suction effect on the pulmonary capillaries which produces oedema or aggravates it. To overcome this effect the application of positive pressure breathing was advised. It has proved to be useful both in cardiac oedema and in the oedema due to inhalation of poison gases. The positive pressure used is from 3 to 6 cm. of water and is applied during inspiration and during expiration. A contraindication is the presence of shock where the venous return to the heart is impeded and where raising the intrathoracic pressure further interferes with the venous return. Favorable results have been observed if positive pressure breathing is carried out with air alone, but the admixture of 40 to 70 per cent of oxygen is more effectual. The closed circuit respiratory mask is a simple means of administering the mixture under pressure. To control expiratory pressure, holes of various sizes are provided on the mask, and the pressure can thus be regulated. In actual treatment the positive pressure should be started at 3 cm. of water and worked up slowly to 6 cm. When discontinuing treatment, pressure is either reduced slowly, or the patient may be tried without the mask for short periods of time which are gradually lengthened. The inhalation of a nebulized spray of 1 per cent epinephrine or 1 per cent Neo-Synephrine at intervals of two to three hours has also been found useful.—*The Treatment of Pulmonary Edema Due to Gas Poisoning in War and in Civilian Life*, A. L. Barach, *New England J. Med.*, February 24, 1944, 230: 216.—(H. Marcus)

**Encapsulated Effusion and Heart Failure.**—Encapsulated interlobar effusion in heart failure is not common. In a series of 368 cases of heart failure, 11, or 8 per cent, showed evidence of interlobar effusion. Effusions of this type are supposedly the result of antecedent infection of the intrapleural space which has resulted in adhesions between the pleural layers leaving the interlobar space the

only locality in which fluid may accumulate. However, encapsulated interlobar effusion is also seen in cases where no infection of the lung or pleura had been present, as far as could be ascertained by history. An alternate theory assumes that it may then be the result of repeated attacks of heart failure with effusion, with deposition of fibrin and eventual adherence of the pleural leaves. Lateral X-ray films frequently serve to distinguish interlobar effusions from tumors of the lung or mediastinum.—*Encapsulated Pleural Effusion Due to Heart Failure*, A. H. Russakoff & T. Weinberg, *New England J. Med.*, March 30, 1944, 230: 370.—(H. Marcus)

**Penetrating Chest Wounds.**—The experiences of a chest surgical team during the African campaign are compiled. In all, 291 cases were treated in three different localities. The impression was gained that cases were handled best when they were treated within two or three days after the injury at a forward base hospital. In field hospitals farther forward not much more can be done than closure of sucking wounds of the chests. Foreign bodies are best not tackled in such a field unit, but are left in place until the patient arrives at the base hospital. In the closure of sucking wounds, tight closure of the deeper layers and loose stitching of the skin is advised, so that drainage may proceed easily. Penetrating chest wounds show different healing tendencies depending on the agent responsible. Stab and bullet wounds heal faster than shell, mine or mortar wounds, and infection is usually less severe. Metallic foreign bodies caused less infection than fragments of bone and clothing. Sulfanilamide was given routinely to patients en route from the front to the forward base hospital. The dose was 2.5 g. every twelve hours. Smaller more frequent doses could not be given due to transportation difficulties. Other drugs, such as sulfathiazole, were not given because it was found impossible to maintain a high enough fluid intake to avoid renal complications. Sulfadiazine might have been most desirable, but was scarce and costly. More

than half the cases, or 187, were complicated by haemothorax. Of these, 62 were infected. It seems best to aspirate the haemothorax as completely as possible without air replacement. A small amount of air may be admitted if the patient's comfort demands it. Infected haemothoraces need drainage. Aspiration is performed daily or every other day until the pus is too thick. Then air-tight intercostal drainage is begun and, when this no longer suffices, rib resection is performed. In empyemata due to trauma, there is no rule as to when it is "safe" to perform rib resection. It is, therefore, preferable to resect the rib under general anaesthesia. The anaesthetist can then administer positive pressure if few adhesions are found and the lung collapses. Water-sealed air-tight drainage is necessary in any case. Pleural foreign bodies may be removed at the time of the rib resection if they are accessible. If not, they are left for a later stage. Clotted haemothorax was found in 6 per cent of the cases. The reason why blood should clot in the pleural cavity is not quite clear, but one of three conditions was usually operative: delay in aspiration, infection or intrapleural foreign body. Clotted haemothorax, unless very small, must be removed. This is done by posterior thoracotomy with resection of an inch of the sixth rib near its angle. The underlying lung may show contusion, atelectasis or pneumonia. Contusion may make the patient very ill but recovery is the rule. The incidence of pneumonia in this series cannot be given because on X-ray examination this condition merges with contusion. Pneumonia in the uninvolved lung was present 10 times. Cerebral complications were rare. They were observed 4 times, 3 of them being due to air embolism and occurring shortly after wounding, and one was due to an infected pulmonary thrombus, twenty-two days after wounding. Foreign bodies within the lung offer special problems, depending on their size and location. Small centrally located foreign bodies are usually left in place. If they are larger than 2 x 1 cm. they must be removed, and also if they are located near the

periphery or near the mediastinum. In this series, 7 intrapulmonary, 7 mediastinal and 14 intrapleural foreign bodies were removed. Wounds involving the abdomen as well as the chest are very serious. In the early stages it may be difficult to state definitely that no abdominal involvement is present. In case of doubt, the general surgeon will prefer to do a laparotomy. The gross mortality in this series was 6 per cent. The figures for a field hospital are considerably higher because more seriously wounded men are seen who never reach the forward base hospital. At a base hospital where patients are admitted about two weeks after wounding their chances for survival are, of course, much better, and the mortality is only 4 per cent. Altogether, 19 patients died, 25 were more or less permanently disabled, and 5 were transferred in poor condition. These figures include a follow-up of two to three months in most cases. The uninfected cases did better than the infected ones. One hundred and twenty-two patients were returned to duty or transferred to convalescent camps. These returned to duty within three months.—*Penetrating Wounds of the Chest*, W. F. Nicholson & J. G. Scadding, *Lancet*, March 4, 1944, 246: 299.—(H. Marcus)

**Rehabilitation of Chest Cases.**—A centre of rehabilitation of medical and surgical chest cases was set up designed to meet the needs of those convalescing from such diseases as pneumonia, empyema, or wounds, and operative procedures. The average patient, upon discharge from the hospital, manifests a marked degree of respiratory inefficiency. This is due to a variety of causes, notably weakness and inefficiency of the respiratory muscles from prolonged bed-rest, damage to the bony thorax, such as malunion of ribs, angulation of ribs and irregularities of new bone formation, and thickening and adherence of the pleura. Inflammatory conditions of the lung are often followed by pulmonary fibrosis, or there may be actual loss of lung tissue, and emphysema of the remainder. Pain during the illness frequently produces a

scoliosis which seriously interferes with chest expansion. When a patient is first admitted to the centre, he is subjected to a complete workup including history and physical examination, chest X-ray and fluoroscopy, and a variety of pulmonary function tests such as determination of vital capacity and its subdivisions, maximum breathing capacity and minute volume. The rehabilitation staff is present at the fluoroscopy and defects needing their special attention are pointed out to them. Measurement of chest and abdominal expansion, and of the vital capacity, are a rough but useful guide to the patient's progress and are repeated every two weeks. The rehabilitation program is administered in classes each of which calls for progressively more severe exercises. The first grade stresses

breathing exercises, and in operative cases these are actually started before the operation, and recommenced immediately thereafter. In the next grade, shoulder movements, bending and rotation movements of the chest are taken up. The higher grades stress bicycle riding, use of pulley and weight machines, foot ball and ball throwing. Later runs of various lengths are added, starting with 200 yards and going up to 2 miles or more. After the course is finished, and when the patient is judged to be as fit as possible, he is subjected to recheck of the physiological tests mentioned above, and to a standard exercise test which measures pulse rate and pulmonary ventilation.—*Rehabilitation of the Chest Case*, F. R. Edwards, *Lancet*, January 15, 1944, 246: 81.—(H. Marcus)



# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Tuberculosis in Selectees.**—The Army plans to exclude active or potentially active cases of tuberculosis. The current program rejects cases of active tuberculosis, cases with scarred infiltrative tuberculosis over 5 cm. in extent by flat film. (Those with lesions of this type under 5 cm. in extent and proven stable over a period of six months are acceptable.) Cases with small calcified lesions may be accepted, but large or numerous calcifications are left to the discretion of the examiner. The total rejectees on the basis of tuberculosis are in the neighborhood of 1.2 per cent. However, the efficiency of the screening process is not perfect. Long and Sterns revealed significant tuberculosis in 10/10,000 for the First Service Command, 13/10,000 for the Second Service Command, 5 and 7/10,000, respectively, for the Sixth and Seventh Service Commands, 36 and 44/10,000, respectively, for the Eighth and Ninth Service Commands. That is, approximately 1500 men in one million had tuberculosis of significance. The causes for these errors were listed as unskilled roentgenologists, obscuring of minimal lesions by bony structures, clerical errors, and speed, fatigue, monotony and strain leading to occasional error even by skilled radiologists. The number of tuberculosis patients at Fitzsimons General Hospital, to which all tuberculous soldiers go unless they have been transferred to Veterans' Administration or discharged to their own care, increased to a peak in March, 1943. A study is now in progress which is analyzing Army discharges from certificates of disability. Thirty per cent of Fitzsimons tuberculosis cases had been discovered within

one month of induction, while 80 per cent had been discovered within six months. Case-finding in the Army consists of induction station X-ray film, X-ray films following onset of symptoms, physical examinations for admission to officer candidate schools, and X-ray films of every man discharged. Thus, over 10 per cent of the total population will have been X-rayed during the physical examinations incident to military service. Approximately 150,000 men will have been rejected for tuberculosis. Most of the open cases will undergo treatment with resultant arrest of a large number of cases and prevention of spread.—*The Occurrence of Tuberculosis in Supposedly Screened Selectees*, A. Freer, *Dis. of Chest*, May-June, 1944, 10: 197.—(K. R. Boucot)

**Tuberculosis in Navy.**—The Navy tuberculosis program includes preinduction X-ray examination, radiographic and clinical studies with the onset of symptoms, instruction in personal hygiene, a well balanced diet and a sanitary environment. There is need for periodic X-ray studies with tuberculin testing when indicated, special studies of factors involved in the increased incidence in the hospital corps, culinary and engine room groups, etc., and an appreciation on the part of all Naval medical officers of the importance of chest X-ray films in the prompt diagnosis of pulmonary tuberculosis.—*Tuberculosis as a Navy Problem*, D. E. Smiley & H. A. Raskin, *Dis. of Chest*, May-June, 1944, 10: 210.—(K. R. Boucot)



**Tuberculosis in Navy.**—By means of fluorography the lungs of 479,373 apparently healthy naval recruits and 23,344 female naval recruits were examined. In the male series, 6,077, or 12.7 per thousand, showed radiographic signs of postprimary pulmonary tuberculosis, and in the female series the figure was 9.1 per thousand. The lesion was classified as minimal in 47.9 per cent of the male and in 55.4 of the female patients. The further care of such a large number of young people with radiographic evidence of minimal tuberculosis presents a serious problem. At first examination in the hospital, only 21 per cent of the male cases were judged arrested. Sixteen per cent could be declared active after preliminary tests were made. The remaining 63 per cent were put into the "doubtful" group and placed under supervision to determine the dynamic status of their lesions. The men were placed on light shore duty and studied extensively with all diagnostic means during a period of hospitalization, varying from three to six months over a two-year period. Of a total of 1,826 cases so observed, 191 eventually developed evidence of active tuberculosis. The incidence was much higher in the age group under twenty and decreased with advancing age. The risk of developing tuberculosis was greatest during the first six months after detection and decreased as time wore on. However, it was practically as great during the second six months' period, the incidence being 6.6 and 5.5 per cent, respectively. This experience teaches that all patients in whom tuberculosis has been diagnosed accidentally need careful work-up and observation over at least a year's time to determine if the radiographically demonstrated lesions are active. Employment under sheltered conditions is advisable during the observation period.—*Management of Minimal Pulmonary Tuberculosis*, W. D. W. Brooks, *Lancet*, June 10, 1944, 246: 745.—(H. Marcus)

**Case-finding in Sailors.**—Five hundred sailors in whom abnormalities of the lungs were discovered on miniature radiograms were subjected to a thorough investigation. Large

films were made and the patients examined clinically, as well as by the usual laboratory methods. None of the patients had reported sick, and those that had symptoms in retrospect reported only those of minimal degree. Physical examination very rarely gave a clue as to the nature and location of the disease and could not be relied upon to make a diagnosis. Of the 500 cases, 134 were classified as fit for duty, 143 were recommended for a three months' observation period on shore duty, active tuberculosis with positive sputum or gastric was present 69 times, active tuberculosis with negative bacteriological findings was present 69 times, tuberculous lesions judged inactive but likely to break down under military service conditions were found 29 times, nontuberculous pneumonitis was present 22 times, and 34 patients were found to be unfit for service because of other conditions. The sedimentation rate was increased in only 27 of the 138 active cases. Tuberculin testing was of no assistance in evaluating the activity of the lesions, unless a change in reaction from negative to positive could be demonstrated.—*Case Finding by Mass Radiography*, A. Kahan & H. G. Close, *Lancet*, May 20, 1944, 246: 653.—(H. Marcus)

**Tuberculosis in Industry.**—Tuberculosis is one of the leading causes of death in the age group which is particularly important as industrial workers. The tuberculosis control office of the Public Health Service assists in mass chest X-ray examinations of workers in war industries and of families in war industry communities. In addition, it assists in transferring the rejected recruits to the local health authorities for further care. Eight transportable 35 mm. X-ray units and two 4 by 5 inch machines were procured for mass radiography. Local X-ray facilities are to be preferred to rapid film methods for small plants. The technique of mass radiography was greatly improved by the use of the Morgan phototimer which eliminates the measuring of the thickness of the chest, the setting of the timer, milliamperage or kilovoltage. Films produced with the aid of the phototimer are of

uniform quality thus facilitating their interpretation and reducing the factor of fatigue of the examiner. The efficiency in detecting early pulmonary lesions increases as one goes from 35 mm. up to 14 by 17 inch celluloid films. The method to be used for a particular industrial survey should be one which benefits the largest number of persons in that industry. During the year and a half prior to December, 1943 the field units of the Public Health Service examined 559,306 persons. Significant reinfection tuberculosis was found in one per cent; 62 per cent of them were minimal, 31 per cent moderately advanced, 7 per cent far advanced. It is important to examine all present employees all new employees and to make periodic reexaminations. The significance of minimal lesions must be carefully evaluated; clinical studies, gastric lavage and comparison films at intervals of several months may be necessary to determine the activity of a minimal lesion. The rehabilitation of the tuberculous worker is of particular importance; sheltered employment, financial security and proper living conditions must be provided by careful planning. The coöperation of the local welfare agencies, the voluntary tuberculosis associations and the labor health committees with the health department and local physicians is necessary to insure a successful program of tuberculosis control. The Public Health Service will assist in the development of control programs by demonstration of new techniques, by offering consultations, by grants for follow-up facilities and by training of professional personnel.—*Conquest of Tuberculosis in Industry*, H. E. Hilleboe & D. M. Gould, J. A. M. A., May 27, 1944, 125: 241.—(H. Abeles)

**Tuberculosis in War.**—Among many factors that have been suggested as influencing the increase in tuberculosis mortality which accompanied the outbreak of war is that of lowered resistance to the disease by those already infected. The author attempted, by means of statistics, to verify this statement. The method of approach was to compare the interval between notification (registration as

an infected person) and death for two periods in which death occurred: (1) the prewar years 1937–1939, and (2) the war years 1940 and 1941. Shorter average duration should appear in the second period if the original postulate is correct. Careful statistical study of these two groups failed to reveal any appreciable difference for either sex. The author therefore concludes that there is no evidence of a lowered resistance to pulmonary tuberculosis at the point at which duration was shortened and, hence, no evidence that lowered resistance was a causative factor in the increase of tuberculosis mortality which occurred in 1940–1941.—*Respiratory Tuberculosis*, E. Lewis-Fanning, Brit. M. J., November 27, 1943, 2: 684.—(D. H. Cohen)

**Tuberculosis in War.**—The authors have come to certain tentative conclusions about the sources of the increase in death from respiratory tuberculosis which occurred in 1940–1941 in England. A review of the statistics revealed that in the period 1923–1939, despite the rapid fall in the numbers of notifications of and deaths from respiratory tuberculosis, the average expectation, for a person just notified, of eventually dying of the disease remained remarkably constant at approximately one-half. Immediately before the war the average expectation of dying within a year of notification was about 22 per cent, and within five years about 44 per cent. Had the incidence of new cases continued to decline as in the pre-war period, instead of increasing, some 6,000 fewer deaths would have occurred during 1940–1943 under normal conditions. Owing to a temporary rise in short-term fatality during the severe conditions of 1940–1941, some 2,500 notified patients probably died in those years instead of in 1942–1943. Another 1,600 notified persons and about 1,000 unnotified persons who in normal circumstances would not have died of the disease at all must have died of respiratory tuberculosis during 1940–1941.—*Wartime Incidence of and Mortality from Respiratory Tuberculosis*, P. Stocks & E. Lewis-Fanning,

*Brit. M. J.*, April 29, 1944, 1: 581.—(D. H. Cohen)

**Tuberculosis in London.**—The author offers a brief note on the morbidity and mortality statistics of tuberculosis in London, reported in the year 1942. This is a follow-up of a previous article covering the years 1938–1942. Analysis reveals that the rates for children have improved compared with 1941. The importance of returning evacuees, improved in health by their stay in the country, is discussed. The incidence of new cases among adults continues to increase, but at a smaller rate. The undiminished pressure of war production, the effects of the black-out on ventilation, and the shortness or absence of holidays, no doubt all contribute to the upward trend. The tuberculosis mortality was considerably lower in 1942 than in 1941. It has been pointed out that the high mortality of 1941 probably has temporarily reduced the proportion of advanced cases within the tuberculous population and that the mortality rate may be expected to rise again when the increased incidence of active disease which occurred in 1940–1941 begins to influence the death rate.—*Tuberculosis in London*, W. A. Daley & B. Benjamin, *Brit. M. J.*, December 4, 1943, 2: 712.—(D. H. Cohen)

**Tuberculosis in Puerto Rico.**—Tuberculosis causes nearly one-half of all deaths between the ages of nineteen and thirty-five in Puerto Rico. In 1933, after twenty years of steadily increasing mortality rates, the peak of 337 was reached. Alarmed public health officials tripled the number of available beds in 1934, but the total thus reached was only 1,500 when, according to National Tuberculosis Association standards, the 5,000 annual tuberculosis deaths called for more than 10,000 beds. Puerto Rico is densely populated and poverty-stricken. Most inhabitants live under crowded slum conditions favoring spread. Without adequate hospital beds, therefore, isolation is impossible, but ambulatory pneumothorax was resorted to in an effort to control open cases. A vigorous campaign for

early diagnosis was conducted. The first pneumothorax clinic was opened in 1935 and, by the end of the fourth year, nearly 2,000 ambulatory cases were being treated. The mortality curve began dropping and, six years after the beginning of the campaign, the mortality rate had dropped 20 per cent. However, in 1941, the death rate was still 245, five and a half times that of the continental United States. Pneumothorax can control a certain number of open cases, but the majority remain a menace unless hospitalized. With the required number of hospital beds, the cost of an adequate program would be 50 million dollars for the first five years, an impossible undertaking for Puerto Rico without federal aid which is now being sought.—*The Tuberculosis Problem in Puerto Rico*, Editorial, *J. Rodriguez Pastor, Dis. of Chest*, September–October, 1944, 10: 447.—(K. R. Boucot)

**Tuberculosis in South Africa.**—The population of South Africa consists of four "races": European, colored, Bantu, Asiatic. In Natal the incidence of tuberculosis in the natives depends on the kind of life they are living: (1) The incidence in those who live a pastoral existence in the tribal reserve is 0.25 per cent. (2) It is 0.75 per cent in those who are more crowded but live a lazy life in the mission reserve. (3) It is 1 to 1.5 per cent in the periurban block belt where the natives work harder. (4) It is 1.5 to 2 per cent among the hard working urban dwellers. The fulminating cases of tuberculosis seen in the gold mines occur in the first few months of a period of work. "Race" *per se* does not seem to be an important factor in the development of tuberculosis; diet and physical effort are probably of greater importance. The three non-European groups have a high death rate. In 1941 in Indians it was five times, in the Bantu seven times and in the colored ten times the European death rate. The death rates of tuberculosis in South African Europeans by age are similar to those in New York. In females between the ages of twenty and thirty, tuberculosis deaths are 15 per cent of deaths from all causes. In males between the

ages of forty and fifty-five, tuberculosis deaths are 12 per cent of deaths from all causes. Lung abscesses are seen frequently in the Bantu race; they are due to aspiration of the vomitus when these people are in coma after beer-drinking celebrations. Amebiasis of the lungs occurs and may closely simulate tuberculosis; the differential diagnosis can be made by the effectiveness of emetine and carbozone in the treatment of amebiasis. Syphilis of the lung is not uncommon in the Bantu and in the Cape colored; the lesions disappear with antisyphilitic treatment. Fungus infections of the lung are seen occasionally. Parasitic infections with *Schistosoma hematobium* and *Ascaris lumbricoides* are very common. Silicosis occurs in people working in the gold mines. Two cases of Loeffler's eosinophilic infiltration of the lungs were seen in Indians. Tuberculosis was spread in South Africa by patients from Europe who came since 1880 to cure. About 1900 there was a great increase of tuberculosis among the natives. The first Tuberculosis Commission was appointed in 1912. In 1919 a Department of Public Health was established. In 1920 the first sanatorium was opened at Nelspoort in the Cape. A Tuberculosis Research Committee was founded in 1925. In June, 1942, 515 beds for European and 2,000 beds for non-European patients with tuberculosis were available. The annual deaths were 750 in Europeans and about 15,000 in non-Europeans. A plan for controlling tuberculosis in South Africa is outlined.—*A South African Team Looks at Tuberculosis*, B. A. Dormer, J. Friedlander & F. J. Wiles, with a Preface by P. Allan, *Proc. Transvaal Mine Medical Officers' Assoc.*, November, 1943, No. 257.—(G. C. Leiner)

**Tuberculosis in Students.**—Tuberculin tests and roentgenological examinations have been compulsory for the students of the medical, agronomic, veterinary and economic sciences of the University of Buenos Aires since 1939. Of a total of 8,186 students, the average of tuberculin-positive was 70.1 per cent among those who entered the University, 70.7 per cent in males and 67.4 per cent in females.

The average rose to 97.5 per cent among the medical students of the sixth and seventh year. Only the latter group could be studied for manifest tuberculosis and 5 per cent of these showed active lesions. The incidence is three to four times higher than that in the other candidates. The increase of tuberculosis is due to the exposure in hospitals and to the living in boarding houses, to the type of life, practical work, sports, extensive plans for study, examinations and competitive activities. The prognosis of tuberculosis in University students seems to be more favorable than in youngsters of the same age and activities of different social strata, owing to better economical standards, to early recognition and treatment of the condition and to the predominantly primary character of the tuberculous lesion.—*Indices de tuberculization de morbilidad tuberculosa en los estudiantes de la Universidad de Buenos Aires*, R. F. Vaccarezza & B. Enquín, *Rev. Argentino-Norte-Americana de Ciencias Medicas*, November, 1943, 1: 714.—(F. G. Kautz)

**Primary Tuberculosis in Nurses.**—Of 3,764 nurses entering training schools, 19.2 per cent were tuberculin-negative. Of the positive group, which comprises 80.8 per cent of all entrants, 30.5 per cent were positive only to comparatively large doses of tuberculin, that is, 1:1000 and 1:100. The number of negative reactors was greater in the younger age groups, amounting to 27.4 per cent in the seventeen year olds. A total of 285 nurses became Mantoux positive within the first year of training, that is, 78 per cent of all nurses who had "Mantoux conversion" did so within the first year of their training. The conversion rate is higher in institutions which do not select their patients but which admit terminal cases of tuberculosis. These nurses also show sensitivity to smaller doses of tuberculin, indicating a more massive infection, and a higher degree of sensitization. No more than 3 out of 10 nurses who became positive had any kind of symptom during the critical period, and it is doubtful whether the symptoms complained of were referable to the

tuberculous infection. Of the 258 cases who showed conversion 33 developed clinical tuberculosis. One of the cases was an extra-pulmonary disease. Six patients developed uncomplicated primary complexes. Two showed only a small pulmonary focus. Three patients developed pulmonary tuberculosis from a progressive primary focus. Pleurisy was present 13 times, in 9 patients with effusion. In 3 cases the pulmonary disease became apparent only after dissemination from the primary focus into other parts of the lung had taken place. Ten patients developed pulmonary lesions which could not be ascribed to the primary complex. They represent reinfection type lesions shortly after the primary infection had taken place. It is felt that the degree of sensitivity of previous nonreactors to tuberculin foreshadows the course the infection will take.—*Primary Tuberculous Infections in Nurses, M. Daniels, Lancet, August 5, 1944, 247: 165.*—(H. Marcus)

**Primary Tuberculosis in Nurses.**—In a previous report by the same author the tuberculin conversion from negative to positive among student nurses was analyzed. The incidence of tuberculosis in initially negative and initially positive students was compared, and the type of disease which developed in the two groups of nurses was analyzed. The tuberculosis morbidity is three and one-half times larger in the initially negative nurses. The annual rate per thousand was 7.4 in tuberculin-positive students and 24.8 in the negative group. This seems to indicate that previous infection with the tubercle bacillus confers a certain amount of specific, though by no means complete, immunity. However, the tuberculin-positive group represents a selected population because the highly susceptibles have been eliminated through disease which either killed them or made them unfit for nursing. Aside from acquired immunity due to previous infection, constitutionally inherited immunity plays an important rôle and explains why under identical conditions of exposure some nurses develop the disease and

some do not. Morbidity following primary infection in student nurses is high. It is doubtful, though, whether it is really higher than in the general population, because the exposure is so much more massive and repeated. The clinical disease may represent secondary infection following closely upon the primary infection. From reports it appears that the tuberculosis infection rate is higher among nurses working in general hospitals than in tuberculosis sanatoria. The answer is found in the better precautions observed in the latter type of institution. In the absence of a reliable method of vaccination which would be the ideal solution to the problem, periodic tuberculin testing of negative reactors at three monthly intervals is indicated. Nurses who show Mantoux conversion should be observed with particular care and should be examined once a month, X-rayed every three months for the first year following conversion, and every six months for the next two years. Strict precautions in handling tuberculous patients and maintenance of a high standard of health and nutrition should be insisted on.—*Primary Tuberculous Infection in Nurses, M. Daniels, Lancet, August 12, 1944, 247: 201.*—(H. Marcus)

**Tuberculosis in the Insane.**—A roentgenological survey of a community of 2,239 patients with mental diseases revealed pulmonary tuberculosis in 3 per cent of the male and 1.9 per cent of the female inmates. During the pre-war decades the female tuberculosis death rate at the same institution (Leavesden) exceeded the male, but since the outbreak of war the contrary has been the case. The author believes there are grounds for the opinion that the mobilization for active service of half the trained male nursing staff may have been a contributory factor. It is concluded that pulmonary tuberculosis constitutes a particularly formidable menace to closed communities composed of biologically inferior and mentally subnormal persons. The danger is increased when wartime circumstances modify their environment and regimen. Under such circumstances, there may be an incidence of

the disease so high that it may assume the proportions of a "local epidemic." Measures to cope with the situation are described. They include roentgenological examinations of all admissions, the segregations of suspects and arrested cases and the culture of stomach washings as a means of diagnosis.—*The Clinical Aspects of Pulmonary Tuberculosis in a Community of Aments*, J. F. MacMahon, *Brit. J. Tuberc.*, January, 1944, 38: 14.—(E. H. Rubin)

**Tuberculosis Control.**—Analysis of the statistics of a large sanatorium demonstrates the well known fact that 90 per cent of all admissions are advanced cases. Only 10 per cent are minimal cases, and the number of patients who are discharged as apparently arrested or arrested is consequently small. The results of sanatorium treatment do not seem to justify the expenditure of public funds were it not for the fact that positive sputum cases are effectively segregated by hospitalization. This end is more important than the treatment of the individual case from the public health point of view. Because tuberculosis is still the most important disease causing death between the ages of twenty and forty, efficient case finding is the answer to the increasing tuberculosis rate. Every effort should be made to locate and treat the early minimal case. The army induction program has contributed towards this goal, but further efforts and funds must be expended in surveys of high school students, food handlers and certain classes of people from lower economic income groups where tuberculosis is known to be prevalent. The mobile X-ray unit may well be sent to districts of cities from where a high incidence is reported and the population may be surveyed by 4 x 5 photoroentgenograms such as are used in the Army. It is essential that such efforts at case finding be accompanied by appropriate laws making it impossible for positive sputum cases to leave the sanatorium at will.—*The Problem of Tuberculosis Control*, J. A. Foley & J. B. Andosca, *New England J. Med.*, July 20, 1944, 231: 86.—(H. Marcus)

**Survival Rates.**—This article is a follow-up of a previous article which investigated 406 adult patients with sputum-positive tuberculosis. The diagnoses were made in the years 1928–1938 and this follow-up carries through 1942. It was observed that in those cases who survived ten years there were no further fatalities. However, nearly half of those who were alive after the first five years failed to survive the second five years. Analysis of the statistics to determine prognosis results in the following. It was found that the probability of surviving five years for the 211 males was 0.26 and for the 195 females 0.25. In summary, it was found that the best outlook is for those in middle life; the young and the elderly fare notably worse.—*Survival Rates in Pulmonary Tuberculosis*, B. C. Thompson, *Brit. M. J.*, December 4, 1943, 2: 721.—(D. H. Cohen)

**Childhood and Adolescent Tuberculosis.**—The author summarizes fourteen years' research work in the field of childhood and adolescent pulmonary tuberculosis and its relation to adult tuberculosis. A series of seven "reports" are summarized. An early "report" (1930) analyzed mortality rates from tuberculosis in childhood for the period 1898 to 1917, in England and Wales, and brought out the following interesting facts: (1) the decline in mortality rate was greatest for children under five years old; (2) abdominal tuberculosis declined rapidly and tuberculous meningitis rose relatively; (3) although the mortality rate due to tuberculosis was greater in infancy than in later childhood, when taken in relation to the mortality rate from all causes, tuberculosis is a much less frequent cause of death in young children than in those approaching adult life; (4) before 1914 the 0–5 year age group had the highest tuberculous mortality; since 1914 the tuberculosis mortality rate has been considerably higher in young adult life and middle age than in infancy; (5) the mortality peak in adult life changed from the forty to fifty year group to the twenty to twenty-five year group; and (6) the importance of exposure in open cases of

tuberculosis was made very apparent. This report emphasized the improved position of tuberculosis in childhood and underlined the continuing and relatively increasing menace of young adult tuberculosis. The second "report" (1931) analyzed tuberculin testing of 1,220 children under fifteen and revealed the importance of contact with open cases. An interesting feature was the revelation that the results of tuberculin testing in a group of children with no history of contact scarcely differed from the results obtained in a group of children with a history of contact with a "closed" case of tuberculosis. The third "report" (1932) analyzed the results of a comparative study of X-ray findings and Mantoux reaction in 500 children. The conclusion here was that typical lesions of the adult type were uncommon in children under fifteen years of age. The fourth "report" (1933) dealt with a reinvestigation of Mantoux positive children. The great majority (96 per cent) remained positive. Sensitivity to tuberculin became more marked in the elapsed time. The figures also revealed that a high degree of sensitivity was reached at an early age in contact children. Whereas in the majority of noncontact children this degree of sensitivity was not reached at any age during childhood. The fifth "report" (1939) dealt with primary tuberculosis of the lungs in childhood and the conclusions reached were: (1) primary infection by tubercle bacilli is uneventful clinically and the lesion formed heals satisfactorily in most cases; (2) immediate and latent complications arise from the inoculant of the lymph nodes; (3) tuberculous meningitis has been, and still is, a serious outcome of tuberculous infection; (4) tuberculous morbidity and mortality in childhood are markedly influenced by exposure to infection; (5) the "adult type" of tuberculosis does not present a serious problem in childhood; and (6) in relation to pulmonary tuberculosis in childhood and even to tuberculous meningitis in childhood, pulmonary tuberculosis in adolescence and early adult life is a greater menace to the population. The sixth "report" (1937) analyzed the family histories of

1,000 patients, who had developed pulmonary tuberculosis, between the ages of fifteen and twenty-five. There was a history of contact in 40 per cent of the cases. Another aspect, constantly making itself apparent, was the advanced stage of tuberculosis reached before treatment was begun or was even sought by the young adult. The follow-up of many cases supported the author's hypothesis that perhaps the extensive lesions of adult disease are really in many cases deposited during adolescence with the accompaniment of slight, or, at any rate, unexplained constitutional disturbance; that these lesions are carried unrecognized, perhaps extending slowly and without symptoms, until they make their presence known in adult life, either by reason of their spread past a definite point or because some environmental cause allowed their reactivation. The seventh "report" (1936) deals with investigation of 2,381 apparently healthy young people between fourteen and twenty-one years old. Here it was revealed that there was a definite incidence of pulmonary tuberculosis in 0.65 per cent and a possible incidence in 1.08 per cent. Here, then, was a means of detecting at a really early stage adolescent lesions which later would give rise to clinical disease, and a means of providing the clinician with material at a stage in which treatment should be easy compared with well established lesions which they cannot hope to cure, but only to arrest. This group of healthy adolescents is a very difficult one to treat. At the present time, they are, when detected, handled in one of the four following ways: (1) they are ignored or merely observed for a period; (2) they are kept under careful observation with improvement in their home environment; (3) they are sent to a sanatorium; and (4) they are treated by artificial pneumothorax. Because of the economic factor, as well as the general disregard for sanatorium treatment in the symptomless adolescent, the author believes that a shallow pneumothorax should be induced in all these cases, bilateral if necessary, and for a period of two to three years. The time element has been too short thus far for a fair appraisal of this form of

treatment.—*Childhood Infection and Its Relation to Adolescent and Adult Pulmonary Tuberculosis: A Record of the Brompton Hospital Research Department during the Last 14 Years*, A. M. C. Macpherson, *Brit. M. J.*, July 24, 1943, 2: 98.—(D. H. Cohen)

**Bovine Tuberculosis.**—The authors reviewed the incidence of pulmonary tuberculosis of bovine origin since 1934 in a series of 2,101 cases treated at a sanatorium. There were 48 cases of bovine origin, or 2.28 per cent. Isolation was by culture on a modified Loewenstein-Jensen medium and in a few instances guinea pig inoculation was necessary. In 2 cases treated by pneumothorax, in which effusions developed, typical bovine tubercle bacilli were isolated from the effusions as well as from the sputum. The incidence of 2.28 per cent is the highest recorded in England, though considerably less than the lowest Scottish figures. No children under fifteen were included in this study. A breakdown of the figures reveals a rate of 2 per 100,000 in the city and urban population and a rate of 16 per 100,000 in the rural population. The methods of infection are three: (1) alimentary ingestion of infected material, most commonly milk, either raw or insufficiently heat-treated; (2) air-borne droplet infection—contact with cattle; or (3) air-borne droplet infection—human to human. In analyzing the series of 48 cases, the probable mode of infection was alimentary in 16 (33 per cent); air-borne cattle-contact in 10 (21 per cent); air-borne familial in 3 (6 per cent) and in 19 cases (40 per cent) no definite evidence could be ascertained as to method of infection. Details are given of three families, in each of which 2 members were found to have pulmonary tuberculosis of bovine origin. The original source of infection in each family was probably contact with tuberculous cattle; and the subsequent infection of the other member was probably due to human transmission of bacilli of bovine type.—*Pulmonary Tuberculosis of Bovine Origin: With Notes on Bovine Infection in Three Families*, I. J. Cutbill & A. Lynn,

*Brit. M. J.*, February 26, 1944, 1: 283.—(D. H. Cohen)

**Tuberculosis in Newborn.**—Congenital tuberculosis is rare. Whether or not the fetus will be infected depends entirely on the type of tuberculosis present in the mother. Isolated pulmonary tuberculosis carries no danger for the fetus, but is extremely dangerous for the newborn infant. When the mother has miliary tuberculosis the fetus is usually affected, but not necessarily so. In protracted hematogenous dissemination with tuberculosis of the endometrium, the fetus is always infected and abortion or stillbirth is the rule. Congenital tuberculosis of the fetus or newborn can only be diagnosed if three conditions are fulfilled. The mother must have tuberculosis, tuberculosis in the child must be proved by organ section or cultural methods and neonatal tuberculosis must have been excluded with certainty. In congenital tuberculosis the primary focus is usually in the liver where it originated through infection via the umbilical vein. However, other types of congenital tuberculosis have been reported. Massive infection may flood the organism through the ductus venosus. Many primary pulmonary foci are then the rule. Another mode of infection is through aspiration or ingestion of infected amniotic fluid. The infected fetus is usually stillborn or survives but a short time. Several cases are known, however, where the mother died of miliary tuberculosis and a healthy child was delivered by Caesarean section shortly before the mother's death. This would seem to be the treatment of choice where the diagnosis of miliary tuberculosis is absolutely certain. It is preferable to perform section before the onset of labor.—*Die prognostische Bedeutung der mütterlichen Tuberkulose für das Neugeborene*, E. Held, R. Rehsteiner & E. Uehlinger, *Schweiz. med. Wchnschr.*, April 8, 1944, 74: 365.—(H. Marcus)

**Lower Lobe Tuberculosis.**—True basal lesions are rare, but lesions in the apex of the lower lobe are quite frequent. The incidence



is given as from 0.5 to 4 per cent of all sanatorium admissions. It is convenient to differentiate between pure and impure lower lobe tuberculosis. In the former, the lesion in the lower lobe is the sole tuberculous focus. In the impure form the lesion in the lower lobe is the active lesion, but fibrotic or minor upper lobe lesions are present. The incidence is greater in women than in men, and the right lung is affected more frequently than the left. The pathogenesis of the pure type is probably an extension of the primary parenchymal focus or of the lymph node component of the primary focus. The impure type is particularly prone to occur in women. Improper ventilation of the apex of the lower lobe may be the key to the pathogenesis in this type of lesion. Bronchogenic spreads to the lower lobes show a good tendency to clear. A spreading lesion in the lower lobes, therefore, spells a bad prognosis. In making a diagnosis of lower lobe tuberculosis, lateral X-ray films must be taken and a positive sputum is a prerequisite for the diagnosis, especially of the pure type. The differential diagnosis includes bronchiectasis, which is difficult to exclude at times, especially when old apical lesions are present. Other diseases to be differentiated are: atypical pneumonias, lung abscess, mycoses, and neoplasms. Treatment of this form of tuberculosis is the same as of upper lobe tuberculosis. In pneumonic lesions it is wise to await cavitation before inducing pneumothorax. Phrenic paralysis alone is not very helpful, but it has a place in conjunction with pneumothorax or thoracoplasty. Thoracoplasties often require the removal of eleven ribs, including the anterior segments, and lobectomy or pneumonectomy would seem a better solution in some cases.—*Tuberculosis of the Lower Lobe*, A. Z. Ossen, *New England J. Med.*, June 8, 1944, 230: 693.—(H. Marcus)

**Treatment of Pulmonary Tuberculosis.**—This article was taken from a Memorial Lecture delivered in honor of Sir Pendrill Varrier-Jones and consists of many and varied remarks about the diagnosis and treatment of pulmonary tuberculosis. The Papworth set-

tlement is particularly stressed. In discussing the selection of patients for different forms of treatment the author differentiates four groups. In the first group, at the time of diagnosis, the patients are immediately suitable for sanatorium treatment. In the second group, which comprises a larger number, the patients will require a period of initial treatment either in a tuberculosis hospital or in the nursing block of a sanatorium. A third group of patients are suitable for treatment in a tuberculosis hospital. Some of them are unlikely to derive benefit in the future from sanatorium treatment; but others, following surgical therapy, will require a period of sanatorium treatment. In the final group of patients the disease at the time of diagnosis is too advanced and extensive for sanatorium treatment; palliative treatment, either in the tuberculosis hospital or at home is required. At Papworth, of primary importance is the fact that the consumptive remains under continuous supervision—medical, psychological and social. He passes through the stages of hospital and sanatorium treatment, and is provided with occupation suited to his state of health. When afebrile he works at a trade, for which he receives the trade union rate of wages. He and his family reside in the village settlement. If at any time his health relapses he is sure of prompt and expert treatment in the institution. Preliminary studies now reveal that none of the children born in Papworth Village have contracted tuberculosis of the lungs, glands, bones, or joints or, indeed, in any known clinical form. There has been no case of tuberculous meningitis. X-ray findings indicate that an appreciable proportion of the children have been infected by tuberculosis like the rest of the adult population. In view of the expected increase in tuberculosis morbidity and mortality following this war, the author suggests expansion of the present facilities of such places as Papworth, so as to take care of the tuberculous veteran and his family.—*The Comprehensive Attack on Pulmonary Tuberculosis*, A. S. MacNalty, *Brit. M. J.*, November 13, 1943, 2: 599.—(D. H. Cohen)

**Lunula of Finger Nails.**—In a previous study done in 202 patients with pulmonary tuberculosis, the tendency on the part of the lunulae to disappear during the disease had been found. The diminution in size of the lunulae was greatest in patients who had tuberculosis and silicosis and in patients who were dyspneic. In this paper the observations on another 230 patients with pulmonary tuberculosis are discussed. One hundred and eighty-eight patients with far advanced and 42 patients with moderately advanced disease are compared with 100 controls. The average width of the lunulae in moderately advanced and in far advanced cases was definitely less than in the controls and in the far advanced cases less than in the moderately advanced cases. The lunulae were absent from all finger nails in the moderately advanced group approximately six times more frequently than in the controls. The lunulae were absent from all finger nails in the far advanced group ten times more frequently than in the controls. These changes are probably due to circulatory disturbances.—*The Lunula of Finger Nails in Tuberculosis*, A. L. Banyai & A. V. Cadden, *Urol. & Cutan. Rev.*, July, 1944, 48: 330.—(G. C. Leiner)

**Pulmonary Tuberculosis and Leprosy.**—The generalized dissemination of Hansen's bacilli and their localization in the lungs is not an infrequent occurrence in lepers. Although Danielsen's theory that the bacillus of tuberculosis and that of leprosy may be particular forms of the same germ which have changed according to the environment is not generally accepted anymore, the association of tuberculosis and leprosy in the same individual appears very frequently. Some claim that leprosy and tuberculosis coexist in as many as 45 per cent of the cases of leprosy. Clinical data and autopsy reports of 12 lepers are presented. Lesions of the respiratory system were encountered very frequently, even in those cases in which there were no clinical signs. Pulmonary tuberculosis was encountered in 5 of those 12 cases. In one case there were pulmonary lesions due to

tuberculosis and lesions which were believed to be due to leprosy. The diagnosis of tuberculosis is very difficult and the importance of inoculation of suspected material into guinea pigs is particularly stressed.—*La tubercolosi polmonare e le localizzazioni lebbrose nei polmoni nel decorso della lebbra*, A. Cherici & G. Rizzi, *Riv. di tisiol.*, 1942, 15: 134.—(G. Simmons)

**Tuberculosis and Atelectasis.**—True atelectasis is the absence of air in the alveoli, owing to intraparenchymatous causes. The most accepted view concerning the mechanism of this process is that of the absorption of the intraalveolar air after the afferent bronchus has been obstructed. There is, however, much clinical and experimental evidence in favor of the more modern concept that sees the cause of atelectasis in an active expulsion of the air from the alveoli. The correct understanding and interpretation of the atelectasis is indispensable to avoid diagnostic mistakes and to conduct properly certain therapeutic procedures. The "lobitis" described by Léon Bernard as a massive sclerotic lesion with extensive pleural adhesions, is very often due to a lobar atelectasis associated with tuberculous lesions, as the possibility of instituting a pneumothorax with selective collapse and the successive complete reexpansion of the lung proves it. The sudden appearance of a massive density, simulating a tuberculous infiltration, may often be caused by atelectasis. The characteristic triangular shadow in the cardiophrenic angle can also be due to pulmonary atelectasis, mostly of the right middle lobe. The presence of a circumscribed area of atelectasis around the pulmonary insertion of a pleural adhesion is a frequent thoracoscopic finding. This type of atelectasis is called by the author "partial acinous atelectasis." The modern view of Viola considers the atelectasis as due to an active contraction of the alveoli, caused by a reflex increase of the physiological pulmonary tonus. The presence of a bronchial obstruction is not always demonstrated in cases of atelectasis. The disappearance of the atelec-

tasis after bronchoscopy in the absence of bronchial obstruction can be explained by the abnormal stimuli brought upon the bronchial tree by the procedure or, rather, by the anesthesia. On the other hand, the observation of breathing areas in an atelectatic lobe speaks also against a purely mechanical origin of the phenomenon. The partial acinous atelectasis suggests a nervous distribution. The inflammation of the serosa may produce an atelectasis through a pleuropulmonary reflex mechanism, even before the appearance of an effusion. Unsuccessful attempts at pneumonolysis, without any modification in the degree of collapse, may be followed by atelectasis. It is not known how and where this reflex mechanism originates; it is, however, admitted that the pleura, the subpleural tissue and the bronchial mucosa may be the regions where the reflex arch is initiated. The contraction of the alveoli would precede the absorption of the air and would represent the essential factor in the atelectasis. Atelectasis can be provoked experimentally by the action of acetylcholine, histamine etc., or by simple irritation of the pleura. The effect of acetylcholine on the alveoli may be demonstrated experimentally and also during thoracoscopic examination. Experimental atelectasis in the guinea pig may assume either the massive type or the disseminated type. The known laws of gaseous exchanges speak also against the theory of a simple obstructive mechanism in the pathogenesis of atelectasis. The absorption of the alveolar air is certainly possible as long as the pulmonary circulation persists, but it could not continue after the equalization of the partial pressures of the gaseous components of the alveolar air and the blood had been obtained. The complete absorption of the alveolar air can only be understood if we admit an active contraction of the alveolar wall; thus, the partial pressures of the components of the alveolar air would be maintained at a level superior to that of the gases of the blood and the process of absorption would continue until it is complete. The existence of a physiological tonus is admitted for other organs, its possible function was disregarded until now only in the case of the lung.

The anatomical substratum of the pulmonary tonus is uncertain: interalveolar muscle plexuses have been found by some authors; the presence of muscle cells in the alveoli is, however, not indispensable to explain their contractility. The capillaries contract without the presence of muscle cells in their walls and it is recalled that capillaries are important components in the alveolar wall. Atelectasis influences the tuberculous process in various manners; pericavitary atelectasis favors the enlargement of the cavity, while atelectasis of an entire lung, or of an extensive part of it, has a beneficial effect on the regression of the lesions. The author thinks also that the mechanism of action of the Monaldi method is the irritating effect of the introduction of the tube and the consecutive atelectasis. Introducing into the cavity a massive rubber band, without the possibility of drainage, he claims to have had the same effect. The subcutaneous injection of small doses of acetylcholine may prove beneficial in certain cases where the Monaldi method has failed. The practice of pneumothorax gives also interesting examples of atelectasis of reflex origin; for instance, the immediate collapse of a lung after the first introduction of air when highly negative readings exclude the possibility of a perforation. The kinking of the main bronchus can also be discarded because of the rigidity of the anatomical structure of it, and also because a film taken in deep inspiration may show a good ventilation of the formerly atelectatic lung. The low intrapleural pressure due to atelectasis of the lung is the cause of the so-called effusion *ex vacuo*. The observation of the sudden reëxpansion of a lung collapsed by pneumothorax is a further argument for the reflex mechanism of atelectasis; in such cases probably antagonistic reflexes enter the scene, counteracting the reflex causing the exaggeration of the pulmonary tonus.—*Tuberculosis y atelectasia del pulmon, C. Xalabarder, Publ. d. Inst. Antituberc. "Francisco Moragas," Barcelona, 1943, 5: 89.*—(L. Molnar)

**Bronchoscopy in Pulmonary Tuberculosis.**—Drawing on their observations in nearly 500 bronchoscopies in a selected group of patients,

the authors have a rather complete set of color drawings to illustrate the various types of lesions encountered. They believe that tuberculosis in the parenchyma is always accompanied by changes in the mucous membrane of the draining bronchus, and that these changes are of the same nature as the pulmonary lesion and vary with the progress of that lesion. Hence the bronchoscopic observation of the varying changes in the bronchial lesion is of utmost importance in the management of collapse therapy. The effects of impaired drainage and ventilation by improperly managed or contraselective pneumothorax are often demonstrable. The method provides additional support to the belief that every pneumothorax should be a selective pneumothorax. The authors do not believe in cauterization of the superficial ulcers visible through the bronchoscope nor in instrumental dilatation of strictures. A large number of illustrative cases are given, showing how bronchoscopy can be of great help in the management of surgical collapse and for this reason make a strong plea that bronchoscopy as a specialty belongs in the field of the chest surgeon, who more than any other can make the most of it.—*Bronchoscopy in Pulmonary Tuberculosis*, M. S. Lloyd & J. A. Burdetti, *J. Thoracic Surg.*, October, 1943, 12: 668.—(W. M. G. Jones)

**Gastric Disturbances in Pulmonary Tuberculosis.**—Thirty-seven per cent of 1200 patients with pulmonary tuberculosis had gastro-enteric disturbances in the early stages of the disease. This percentage rose to 65 per cent if cases with anorexia as the sole gastric symptom were included. Dyspeptic symptoms were present in 42 per cent of cases of exudative and 18 per cent of cases of fibrotic disease. In the majority of cases there was gastric hyposecretion, hypoacidity and hypomotility. Salivary secretion also was diminished.—*Le disfunzioni gastro-enteriche nella tubercolodi polmonare*, M. Valli, *Riv. di fisiol.*, 1941, 14: 287.—(G. Simmons)

**Miliary Tuberculosis.**—Forty-one cases of acute miliary tuberculosis were seen at the

Hôpital Laval at Quebec. The age of the patients was between five and forty-nine years, 22 patients were eleven to twenty years old. There were 25 female and 16 male patients. Miliary tuberculosis was seen in city dwellers as often as in persons from rural districts. Thirty-one patients were observed until death; of these, 11 developed meningitis. Tubercle bacilli were found in the sputum in 20 cases, in the gastric lavage in 7 cases. Autopsies were done in 9 cases: in all of them pancreas and myocardium were free from tuberculosis.—*A propos des granulies aiguës*, R. Desmeules, L. Rousseau & P. Richard, *Laval méd.*, October, 1944, 9: 633.—(G. C. Leiner)

**Chronic Miliary Tuberculosis.**—Chronic miliary tuberculosis ("*granulie froide*") is rare. The diagnosis is possible only with the help of the X-ray picture. Two cases are reported: (1) A twenty-one year old man developed bilateral tuberculous pleurisy in 1936 and 1937. In 1942 a chest X-ray examination showed reticular and nodular infiltrations in both subclavicular regions. In April, 1943 these lesions were seen throughout both lungs. The patient lost 4 lbs., his temperature was never above 99°F. There was no cough, no expectoration. The patient died in June, 1943. (2) An eighteen year old man developed tuberculous epididymitis in August, 1941. One month later he started to cough and to run fever. A chest X-ray examination revealed numerous nodular and reticular shadows throughout both lungs and pleural effusion on the right. Within a year the infiltrations disappeared and in June, 1943 the chest X-ray showed no abnormalities. In February, 1944 the patient again developed cough. The chest X-ray showed soft infiltrations above and below the left clavicle. Chronic miliary tuberculosis can (1) disappear completely, (2) transform into caseo-cavernous or fibrotic tuberculosis, (3) turn into acute miliary tuberculosis.—*La granulie froide*, R. Desmeules & P. Richard, *Laval méd.*, October, 1944, 9: 625.—(G. C. Leiner)

**Intrapulmonary Injections in Tuberculosis.**—Intrapulmonary injections of 2 cc. of car-

bolic acid have been advocated for the treatment of pulmonary tuberculosis by Roberts in British India since 1937. The author has practiced this method and he feels that the results have been satisfactory. After careful selection of the pulmonary area by stethoscopy and roentgenography, several injections in various spots are serially repeated. Although the method has not found any appreciable notice or recommendation by the Tuberculosis Association of India, the author suggests a fair trial. There is no technique described nor are the claimed results supported by statistics.—*Rôle of Intrapulmonary Injections in Tuberculosis in India*, S. Swaroop, *Indian M. J.*, September, 1943, 37: 128.—(F. G. Kautz)

**Diasone Reaction.**—A patient with far advanced pulmonary tuberculosis received a total of 28.67 g. of diasone within a period of three weeks. On the twenty-second day of chemotherapy the patient developed a maculopapular eruption of the skin, sore throat and fever up to 102° F. The rash spread all over the body including the mucous membranes of the mouth and became vesicular and bullous in character. Six days after its appearance the rash disappeared with generalized exfoliation. The patient gave a history of having been treated with 2 g. of sulfonamide for four days about a year prior. At that time she developed a rash without systemic reaction. The reaction to diasone is interpreted as an idiosyncratic one. It was the only serious reaction to diasone encountered in a series of 63 patients.—*A Severe Reaction following Administration of Diasone*, K. H. Pfuetze & Marjorie M. Pyle, *J. A. M. A.*, June 3, 1944, 125: 354.—(H. Abeles)

**Miliary Tuberculosis of Pharynx and Larynx.**—Miliary tuberculosis of pharynx and larynx has been described by Isambert in 1876. Two cases are reported: (1) The female patient complained of pain in her throat in December, 1942. A short time later she developed dysphagia and lost weight. Laryngological examination at the end of January,

1943 revealed a large superficial ulceration surrounded by fine granulations which extended over the soft palate, the pillars, tonsils, epiglottis and arytenoids. The diagnosis of miliary tuberculosis of the pharynx and larynx (*maladie d'Isambert*) was made. A chest X-ray examination showed some small shadows in the second and third left interspaces; one week later fine nodular shadows were seen throughout both lungs. The physical examination of the lungs gave normal findings. The patient died after one week. (2) An eighteen year old female patient was admitted on April 29, 1943, with moderately advanced caseo-cavitary tuberculosis of the lungs. In September, pharynx and larynx were found normal. In November the patient developed pain in her throat. On December 13, 1943, fine granulations and ulcerations were found on tonsils and pillars, and the diagnosis of miliary tuberculosis of pharynx and larynx was made. The patient became dysphagic and, at the end of December, there was a large superficial ulcer over the soft palate, tonsils, posterior wall of the pharynx. The patient became cachectic and died on January 11, 1944. Miliary tuberculosis of pharynx and larynx (*granulie pharyngo-laryngée, maladie d'Isambert*) is not rare. It runs an acute course. It starts in the pharynx and spreads later to the larynx. The main symptoms are dysphagia, asthenia, loss of weight, cachexia. The usual treatment of laryngeal tuberculosis is of no avail in these cases.—*La granulie pharyngo-laryngée*, G.-L. Coté, *Laval méd.*, October, 1944, 9: 641.—(G. C. Leiner)

**Laryngeal Tuberculosis.**—On the basis of his vast experience the author is an enthusiastic supporter of attinotherapy for the treatment of laryngeal tuberculosis. Cemach's lamp has given the best results, but it is emphasized that general sanatorium care, in addition to the local treatment, is absolutely essential. Of 148 patients treated with this lamp, 90 were followed over "a long period of time," 46 were cured, 20 remained stationary and 24 "turned negative." The treatment consisted in irradiation of the laryngeal lesion

tor twenty to thirty seconds at weekly intervals. The total number of treatments was dependent upon the type of lesion present. In the majority of cases, however, considerable improvement was noticed after four or five treatments. The lamp and the technique of its use are described.—*Cura della tubercolosi laringea con la lampada di Cemach, F. D'Onofrio, Riv. di fisiol., 1940, 13: 41.*—(G. Simmons)

**Bronchial Tuberculosis.**—Tuberculosis of the trachea and main bronchi is comparatively rarely found at autopsy. Out of 206 consecutive autopsies, only 8 cases showed tuberculosis of the main bronchi and 2 of these had tuberculosis of the trachea as well. The incidence, therefore, is less than 5 per cent. All cases showed active cavitary tuberculosis with positive sputum. Primary tuberculosis of the trachea or main bronchi, in the absence of pulmonary tuberculosis, is practically unknown. It is likely that a local nonspecific damage to the bronchial wall precedes the development of tuberculous disease. Sputum clings to the damaged surface more easily than to the intact epithelium and constant contact with a bacilliferous sputum sets up the specific process. Pathologically four types of bronchitis are differentiated, but practically these types often show transition into each other. Caseous necrotic tuberculosis of the bronchus frequently gives rise to highly positive sputum and bronchogenic dissemination. Complete obstruction may occur in this type through blockage of the bronchus in the diseased region with caseous material, blood or mucus. The other three types, ulcerative productive disease, productive sclerosing involvement and hyperplastic tuberculosis, more often cause stenosis of the bronchus rather than complete obstruction or occlusion. However, any one of the three last named types may eventually lead to complete fibrous occlusion with atelectasis and shrinkage of the lung, with or without bronchiectasis as its consequence. It is important to differentiate obstruction from occlusion, and these again from compression from without. Compression of bronchi is frequently caused by

enlarged lymph nodes; this is often seen in children and produces atelectasis of the lung or part of the lung. Reaeration with complete disappearance of the shadow is seen as the lymph node decreases in size and the compression is relieved. Although bronchial occlusion is considered an important factor in cavity healing when it affects the bronchi draining cavities, it is doubtful that occlusion of the main bronchi ever leads to cavity healing. The more usual course is infection behind the blockage resulting in bronchiectasis and suppuration. But even then the tuberculous process may disappear and only the results of secondary infection remain behind.—*Tuberkulose der Stammbronchien und tuberkulöse Bronchostenose, W. Berblinger, Schweiz. med. Wchnschr., April 8, 1944, 74: 348.*—(H. Marcus)

**Tracheobronchial Tuberculosis.**—In sanatoria where bronchoscopy is employed routinely, this complication of pulmonary tuberculosis is seen in from 10 to 15 per cent of all admissions. At autopsy tracheobronchial tuberculosis is much more frequent, principally because of the type of case that is autopsied when pulmonary tuberculosis is the cause of death. Clinically, four types of tracheobronchial tuberculosis can be distinguished, the discrete ulcer, the granulomatous ulcer, the tuberculoma and the diffuse bronchitis. The latter type is characterized by generalized redness without definite ulceration. The disease is more common in women than in men, supposedly due to the difference in respiration. The diaphragmatic type of breathing in men encourages better passage of air through the tracheobronchial tree. The lesions are usually found on the posterior wall of the trachea or bronchi. This is due to the horizontal position of the patient who is ill with pulmonary tuberculosis. Frequent and prolonged contact of the bronchial wall with tuberculous sputum seems to predispose to the development of bronchitis. The diagnosis should be suspected in any case where cough is out of proportion to the amount of pulmonary disease, where the sputum is bacil-

liferous out of proportion to the disease as seen on X-ray films, when constant rhonchi are found on physical examination, when the patient has asthmatoïd attacks or when he is subject to attacks of acute cyanosis. The prognosis of pulmonary tuberculosis complicated by bronchial disease is bad. The mortality of such patients is higher, their cure is more prolonged and collapse therapy is more often ineffective. Bronchoscopy is important both in diagnosis and treatment. All patients should be bronchoscoped before they are subjected to collapse therapy because pneumothorax or phrenic crush seem contraindicated in high-grade stenosis. Bronchoscopy may be a life saving procedure in cases where severe stenosis has developed as a result of healing. Some specialists prefer not to treat endobronchial tuberculosis but rely on improvement of the general condition and energetic treatment of the underlying pulmonary lesion to cure the bronchial disease. Others advocate and use local application of the electrocautery or silver nitrate in solution from 5 to 20 per cent.—*De la tuberculose trachéo-bronchique*, J. P. Secretan, Schweiz. med. Wchnschr., April 8, 1944, 74: 359.—(H. Marcus)

**Tracheobronchitis and Allergy.**—At the Wisconsin General Hospital 100 patients with proved tuberculous tracheobronchial lesions were investigated to see if there was any clinical evidence of an allergic diathesis in these cases. Their deductions are as follows: "(1) Patients with tuberculous tracheobronchitis reacted more strongly to routine allergen skin tests than did tuberculous patients without such lesions. (2) Tuberculous tracheobronchitis occurred more frequently in women than in men. The most serious bronchial lesions occurred predominantly in women patients with clinical evidences of allergy. (3) Patients with tuberculous tracheobronchitis were not unusually reactive to tuberculin by skin test. However, those who were most sensitive to tuberculin were most sensitive also to the routine allergens by skin test. (4) There was a general correlation between a

personal history of allergy and a positive reaction to routine allergens, although most patients with a negative personal history reacted to some allergens. There was an apparent direct relationship between a personal history of allergy and the presence of tuberculous tracheobronchitis. (5) Clinical evidence of tuberculous tracheobronchitis correlated well with the finding of bronchial lesions by bronchoscopy; eosinophilia did not. Reaction to the routine allergens did not correlate well with clinical signs. (6) Attempts to desensitize patients with tuberculous tracheobronchitis, using tuberculin, do not seem indicated. Attempts to control an allergic process by desensitization to any pertinent routine allergens, or by other effective means, seem legitimate and indicated."—*Allergy and Tuberculous Tracheobronchitis*, W. H. Oatway, Jr., J. W. Gale & W. A. Mowry, J. Thoracic Surg., February, 1944, 13: 1.—(W. M. G. Jones)

**Pleurisy.**—Out of 2,940 tuberculous patients, 44.2 per cent (males: 38.9 per cent, females: 49.4 per cent) had pleurisy with or without effusion prior to the onset of the parenchymal disease; 55 per cent of hematogenous tuberculosis, 32.5 per cent of infiltrative pneumonias, 52.7 per cent of hilar adenopathies and 100 per cent of extrapulmonary tuberculosis had shown, in the absence of preëxisting pulmonary lesions, pleurisy as the first sign of tuberculosis.—*Frequenza della pleurite quale manifestazione clinica della tubercolosi post-primaria*, D. Onofrio & G. Vendetti, Lotta contro la tuberc., 1939, 10: 213.—(G. Simmons)

**Pleurisy.**—Of 2,896 patients with tuberculosis, approximately 33 per cent had previously suffered from pleurisy with or without effusion. Tuberculosis following pleurisy was more frequently found in females than in males. No predilection for a certain age group was noted. Parenchymal manifestations arose most frequently within two years from the onset of pleurisy. Pleurisy must be considered tuberculous.—*Rapporti patogenetici*

*tici fra pleurite idiopatica e tubercolosi e loro importanza ai fini della prevenzione e assistenza, G. Leoncini, Difesa sociale, 1939, no. 6, 561.—(G. Simmons)*

**Pleurisy.**—Out of 297 children with active primary complexes or with enlarged hilar lymph nodes, 18 subsequently developed pleurisy with effusion. On the basis of this observation the author believes that the majority of cases of pleurisy with effusion in childhood are part of the evolution of the primary complex. In adults, too, pleurisy with effusion often is due to tuberculous foci in hilar lymph nodes. In those cases in which the clinical symptoms are few and X-ray examination fails to reveal disease, except for enlarged hilar shadows, the pleurisy starts probably as a perifocal reaction, first limited to the mediastinal pleura and later extending to all of the pleural cavity. Several X-ray films taken before and after the onset of the disease are presented.—*Sulla patogenesi della pleurite tubercolare, M. Accorimboni, Riv. di tisiol., 1940, 13: 285.—(G. Simmons)*

**Pleural Infections with Gas Bacillus.**—The medical literature contains few references to clostridium infections of the pleural space. These organisms may be found frequently in the sputum of patients with pulmonary tuberculosis, and occasionally in other bronchial secretions. An empyema due to the gas bacillus may therefore develop after lobectomy or in war injuries of the chest. These intrapleural infections, however, do not have the rapidly invasive character or the high mortality commonly associated with gas bacillus infection in injured muscles. The mortality rate in these cases is no higher than in other types of empyema. The treatment most effective is adequate drainage.—*Intrapleural Infection with Clostridium Welchii, J. K. Poppe, J. Thoracic Surg., August, 1944, 13: 340.—(W. M. G. Jones)*

**Radiology of Pleura.**—Radiological technique designed to better visualize the pleura as well as the interpretation of X-ray pictures thus obtained is discussed. The following

projections are described: (1) cranio-dorso-ventral projection of Palmieri in which the direction of the X-rays is parallel to that of the ribs; (2) oblique projection of Lenarduzzi; (3) oblique monolateral tangential projection of Bagliani; (4) monolateral tangential caudo-ventro-dorsal projection introduced by the author. (The latter two are variations of the original position of Palmieri.) X-ray pictures obtained in these positions show the costal pleura which appears as a thin line and is called *stria opaca limitante di Correra* (Correra's opaque limiting line). Under normal conditions this line presents a slight convexity in the intercostal spaces, particularly in the upper part of the thorax. Straight lines and irregular lines are indicative of disease which finds its maximum expression in "Palmieri's opaque marginal band" (*bandelletta opaca marginale di Palmieri*) and which corresponds to the shadow described by Fleischner in X-ray films taken in the postero-anterior position. The diagnostic importance of such pictures is briefly discussed.—*L'indagine radiologica della pleura nella sua porzione costale, L. Pigorini, Riv. di tisiol., 1940, 13: 78.—(G. Simmons)*

**Pleurisy with Effusion.**—Unless another etiology can be proved beyond doubt, all exudative pleurisy must be considered tuberculous. Careful bacteriological studies, including not one but many cultures and guinea pig inoculations, will prove the tuberculous nature of such effusions in a much higher proportion of cases than is generally reported in the literature. Although various investigators have reported different figures, on the average of 73.5 per cent of all patients with exudative pleurisy show parenchymal X-ray changes due to tuberculosis. Depending on the method and number of examinations done, from 40 to 70 per cent of all effusions will yield tubercle bacilli. Pleurisy with effusion is an important manifestation of pulmonary tuberculosis. Thirty-three per cent of patients with pleurisy become ill with clinical pulmonary tuberculosis and, of these 33 per cent, 39 per cent die of their disease.



It is usually an easy matter to diagnose the effusion, but it is much more difficult to diagnose the underlying pulmonary lesion. Yet this is of the greatest importance in every case. Work-up has to include careful and if necessary repeated X-ray examination of the lungs after removal of the fluid, and repeated sputum examinations. When no sputum is available for examination, iodine may be given as a provocative, or gastric lavage is to be performed. Treatment of the effusion is of utmost importance because the future function of the underlying lung depends on it. If important lung lesions are found, the consensus is to replace fluid by air and maintain pneumothorax. However, even if no parenchymal lesion is found, replacement of fluid by air is advised. This avoids symphysis between the pleural leaves and prevents the formation of adhesions. Such treatment will prove extremely useful in the case where pulmonary tuberculosis demands institution of a pneumothorax at a much later date. Aside from this, obliteration of the potential space between the layers of the pleura cripples the patient's respiratory function and reduces his breathing capacity seriously. If, at a later time, collapse therapy is indicated on the opposite side, such treatment may have to be withheld because of marked reduction in respiratory function due to antecedent pleural effusion. Replacement of fluid with air and maintenance of pneumothorax until the inflammation subsides preserve the respiratory function of the lung and, if pneumothorax should become necessary at a later date, it can usually be given. It is advised that the fluid be aspirated during the second week of the effusion. At this time the fever is no longer high and the fluid does not accumulate rapidly. All fluid should be removed at once and be replaced by 200 to 300 cc. of air at intervals while the fluid is removed. Finally air is withdrawn again so that only a small pneumothorax space is maintained. This is to be refilled for two or three months providing the space remains dry. If fluid reaccumulates it is to be aspirated with air replacement, and pneumothorax is continued until two or

three months of treatment with a dry space have been given. Because pleurisy with effusion is just one phase of pulmonary tuberculosis, sanatorium treatment over and beyond the few months necessary to cure the effusion is advised. Within one year 10 per cent of all patients with effusions develop clinical tuberculosis.—*Etiologie, prognostic et traitement de la pleurésie exsudative*, D. Michetti, Schweiz. med. Wchnschr., April 8, 1944, 74: 354.—(H. Marcus)

**Intercostal Nerve Block for Pleuritic Pain.**—In 14 patients who suffered from severe pleuritic pain from pneumonia or pulmonary infarct, intercostal nerve block was performed. The pain was relieved within five to ten minutes following the injection. In 13 patients the relief was permanent, in one reinjection of the nerve was successful and in one reinjection combined with morphine medication resulted in complete relief from pain. The prolonged relief obtained by the treatment cannot be ascribed to the anesthesia alone. The increase in the depth of the respiration following the disappearance of the pain, that is, the increased motion of the pleura may be connected with the permanent relief from pain. The injection is given in the posterior axillary line or anterior to it, corresponding to the intercostal spaces over which tenderness can be elicited. Two cc. of a one per cent solution of procaine hydrochloride were used.—*The Relief of Acute Pleuritic Pain by Intercostal Nerve Block*, H. J. Price, J. A. M. A., November 6, 1943, 123: 628.—(H. Abeles)

**Azochloramid-T in Tuberculous Empyema.**—The technique used by Palitz was adopted in the treatment of 32 consecutive tuberculous empyemata. Reëxpansion was achieved in 65.2 per cent of cases without patent bronchopleural, the results comparing favorably with other methods of treatment. The usual sequence of events is that the fluid which at first is thick and purulent and contains tubercle bacilli, gradually becomes thinner. The tubercle bacilli become more scanty and are first absent on direct examination and later on

culture. No serious reactions or complications were encountered as a result of the irrigating fluid. Occasionally there has been a moderate pyrexia which always settled in twenty-four hours.—*The Use of Azochloramid-T in Tuberculous Empyema*, D. Munro-Ashman & M. G. Tate, *Tubercle*, November, 1943, 24: 181.—(E. H. Rubin)

**Female Genital Tuberculosis.**—Data are presented of 62 cases of proved genital tuberculosis admitted to the University of Michigan Hospital during the last twenty years, with follow-up studies on all cases. There were no clinical signs or symptoms pathognomonic of pelvic tuberculosis. Sixty per cent of the patients were in the childbearing age. Forty-three and one-half per cent of the married patients had not conceived. One-half of the patients (51.6 per cent) revealed no evidence of active extragenital tuberculosis. When operative treatment is indicated, all the genital organs including the cervix should be removed if possible, even though the latter appears grossly normal. Wound complications (infection and fistulae) are much more common after incomplete operations. Seventy-four per cent of the patients in this series are alive an average of 10.5 years after their first admittance. Fifty-four per cent of the survivors claim good health with no untoward symptoms.—*Genital Tuberculosis in the Female*, R. L. Haas, *Am. J. Obst. & Gynec.*, July, 1944, 48: 69. (Author's summary.)—(G. C. Leiner)

**Pelvic Tuberculosis.**—Scant concern has been given roentgen therapy of pelvic tuberculosis in the female in this country as compared with its wide utilization in Europe. Only a few United States persons have reported cases; among these are Lord, Polak, Smitz, Jameson, Linz and Corscaden. All but 22 of 258 references listed by Bickenbach are German, and the majority of the remainder are French. In 1898 Ausset and Bedart reported a successful treatment of peritoneal tuberculosis resistant to other forms of therapy. In 1907 Bircher reported 26 cases of tuberculous

peritonitis improved or cured by X-ray. Since this period little attention appears to have generally been given this method, it having been revived only sporadically in some clinics. Tuberculosis of the genital tract in women is frequently also accompanied by peritoneal tuberculosis. Disease of endometrium alone is unusual and Novak believes it is always secondary in disease in the tubes, while Bickenbach believes it is present in 50 to 70 per cent of cases with tubal disease. The commonest type of tuberculous pelvic disease is tuberculosis of the tubes and pelvic peritoneum or a combination of the two. Smitz says that 3 per cent of female cadavers show genital tuberculosis and 10 per cent of chronic tubal inflammation is tuberculous. The author reports only 94 cases of pelvic tuberculosis on 27,160 gynecological admissions at Woman's Hospital. Surgical treatment is of two types, the conservative, removing only diseased tissue, and the radical favored by many because of the impossibility of determining the extent of the disease macroscopically. Other surgical procedures include laparotomy for diagnosis and removal of pus and fluid and aspiration of ascitic fluid. X-ray procedures include primary X-ray therapy, irradiation after conservative and radical surgery and irradiation of recurrences. Primary treatment is of limited value as some sort of surgical procedure will be required for most cases for diagnosis, and the treatment of supposed tuberculosis seems completely unwarranted. No adequate diagnosis can be made in most cases without curettage or exploratory laparotomy. Having determined the presence of the disease, the question presents as to the value of X-ray therapy as weighed against further surgery or combined with it. Gauss and Gal both believe that early disease does well with either surgery or X-ray while late cases do poorly with either. However, a clean, apparently successful operative removal may be followed by recurrence for which X-ray therapy may be effective. Surgeons prefer to operate from mental habit and because they consider surgery a shorter procedure. However, against surgery

is the operative mortality, the occurrence of postoperative fistulae, the possible production of miliary disease, the danger of injury of bladder and rectum and the likelihood that tissues left behind may be already involved. X-ray has no effect on pyosalpinx, ascitic fluid or abscess material and should be avoided in pregnancy. It is most successful in the dry form of peritoneal tuberculosis but is also of benefit postoperatively after removal of fluid and debris. Protection of ovaries also should be considered in the childbearing period. Mixed infections should be considered on individual merits. When disease of endometrium alone is diagnosed and no symptoms referable to tubes or peritoneum present, it is probably best to try X-ray as primary procedure. When there are frankly diseased tubes, removal followed by irradiation is the method of choice, and in advanced tubo-peritoneal disease, combined treatment is also preferred. The worst prognosis is in cases of severe disease elsewhere although patients may obtain palliation of symptoms from X-ray treatment. Attempts to evaluate results from various clinics are difficult because of frequent indefinite criteria for success. However, Wesseling, reporting X-ray series of 115 cases, reported 66 cures and 24 improved. Gragert reported 44 cases with 22 cured, 9 improved and 5 dead. Bickenbach collected 910 cases from literature of which 617 received irradiation and 293 surgical treatment, his figures giving an excellent showing in favor of X-ray treatment repeated weekly for two to four times and with several cycles at varying intervals. Multiple foci are frequent. Large portals are common, and the author finds it difficult to understand their popularity except in wide-spread peritonitis, and even here he prefers to divide the abdomen into smaller fields. His dosage technique has varied over the years, but recent cases received 75 to 100 r, treatments not being repeated more than once a week. Eleven cases are reported by the author illustrating different treatment and stages of disease, including 4 cases of pelvic peritonitis, 6 with pelvic masses, 3 of which recurred after radical surgery and all 6 masses

disappeared completely after irradiation. Four cases were improved symptomatically but were considered unsatisfactory in the end. One showed little improvement. Technique varies greatly. Gal prefers radium. X-ray dosages vary from the old "tuberculosis dose" to 5 per cent E.D., the average for many being 10 to 15 per cent E.D. Bickenbach gives 50 to 100 r tissue dose with doses and time interval varied according to need of patient and recommends larger doses to produce quick freedom from pain. Some use an anterior and posterior field. In conclusion, the author recommends X-ray therapy in adequately diagnosed cases of pelvic tuberculosis, removal of grossly diseased tubes and primary irradiation of endometrial disease. He feels X-ray is especially effective in localized recurrence following surgery.—*Roentgen Therapy of Pelvic Tuberculosis in the Female*, H. C. McIntosh, *Radiology*, January, 1944, 42: 48.—(G. F. Mitchell)

**Pelvic Tuberculosis.**—Tuberculosis of the reproductive system is the cause of sterility in approximately 10 per cent of female patients who seek advice in sterility clinics. These patients rarely present symptoms referable to the lower abdomen or pelvis. Among a series of 12 patients who were proved to have tuberculosis of the genital tract at laparotomy, only one complained of occasional attacks of lower abdominal pain. Physical findings are frequently normal or minor in comparison with the extent of disease. In this series of 12, 3 patients had negative examinations, 2 had the findings of retroversion and in only 7 adnexal disease was diagnosed. At operation, 6 patients had tuberculous salpingitis, 4 had pyosalpinx and tuberculous peritonitis and 2 had peritonitis and endometritis. Usually nothing can be done to relieve sterility, and adoption is advised. Operations are useful to remove the tuberculous focus provided adhesions are not too extensive. Ultra-violet radiation and X-ray therapy may be of value in some cases. Of the 12 patients covered in this report, none had signs of tuberculosis elsewhere in the body.—*Die*

*Erfassung symptomlos verlaufender Unterleibstuberkulosen bei der Sterilitätsbehandlung, H. Scherer, Schweiz. med. Wchnschr., April 8, 1944, 74: 358.—(H. Marcus)*

**Tubal Pregnancy in Tuberculous Salpingitis.**—Although both tubal pregnancy and tuberculous salpingitis are fairly common, the combination of these two is a rarity, probably because of (1) complete obstruction of the lumen of the tube, (2) lack of nutrition to fertilized ova, (3) difficulty in nidation owing to lack of healthy mucosa. The author describes the case of a thirty-five year old white female, in whom tubal pregnancy occurred first on the right, and then, two years later, on the left side. Histological examination revealed tuberculous salpingitis on both sides. The patient also had endometrial tuberculosis and inactive pulmonary tuberculosis.—*Recurrent Tubal Pregnancy in Tuberculous Salpingitis, H. A. Pink, Am. J. Obst. & Gynec., September, 1944, 48: 427.—(P. Lowy)*

**Renal Tuberculosis.**—Renal tuberculosis is associated with extrarenal tuberculous lesions in a large percentage of cases. The incidence of calcified mesenteric lymph nodes in cases of tuberculosis of the kidney is 13 per cent, where as it is only 6 per cent in patients with nephrolithiasis unassociated with tuberculous lesions. Tuberculous epididymitis and prostatitis are found in 42 per cent of cases with renal tuberculosis, whereas no case was found in a control series of 93 patients with nephrolithiasis. Evidence of healed or active reinfection type of pulmonary tuberculosis was associated with tuberculous kidneys in 34 per cent of the cases, as contrasted to 4 per cent in the nontuberculous group. Healed primary complexes were present in the same percentage of cases in both groups. Knowledge of the frequent occurrence of extrarenal tuberculosis in cases of renal tuberculosis should facilitate arriving at a definite diagnosis.—*Extrarenal Tuberculous Lesions Associated with Renal Tuberculosis, D. S. Cristol & L. F. Greene, New England J. Med., September 21, 1944, 231: 419.—(H. Marcus)*

**Tuberculous Peritonitis.**—This condition is difficult to diagnose clinically. Acute and chronic forms are recognized. Acute peritonitis may be part of a generalized miliary tuberculosis or it may be localized due to infection from a neighboring lymph node. Chronic peritonitis may result from perforation of tuberculous ulcers, from lymphatic channels or from blood-stream dissemination. The amount of exudation depends on the activity of the process. In the end all cases of peritonitis tend to be dry and adhesions are the rule. The loops of intestine are matted together and the mesentery becomes enormously thickened. Simultaneous involvement of the uterine tubes is frequently seen, leading to speculation as to whether a tuberculous salpingitis could at times be the source of peritonitis. Clinically the patient presents complaints of vague abdominal pain which is rarely severe, weight loss, and fever which may be low grade or septic in type. Abdominal distention due to fluid may be quite marked. X-ray examination of the gastrointestinal tract may enable the roentgenologist to make a definite diagnosis. A scout film of the abdomen shows low grade ileus with or without fluid. Studies of the large intestine with barium show the colon to be fixed in position. After evacuation of the barium enema it retains its low location even after the patient assumes the upright position. Studies of the small intestine also show a lack of normal motility. The barium passes through abnormally rapidly. The loops of bowel are matted together, and the spaces intervening between the loops are frequently widened.—*Roentgen Features of Chronic Tuberculous Peritonitis, J. J. McCort, Arch. Surg., August, 1944, 49: 91.—(H. Marcus)*

**Intestinal Malabsorption with Tuberculosis.**—A sixteen year old white boy was first seen in 1935 when he gave the history of increasing diarrhea for the past two years. As an infant, he had been fed raw milk from a tuberculous cow. In the following years the diarrhea became worse and the patient developed edema of the legs and face, and soreness of

the tongue. In 1940 the symptoms of tetany appeared. Laboratory examinations gave similar findings to those in the sprue syndrome: There was hypoproteinaemia, hypocalcemia, a flat oral dextrose tolerance curve, steatorrhea; however, there was no anemia, no achlohydria, a decreased basal metabolic rate and roentgen evidence of increased motility of the gastrointestinal tract. Kidney and liver functions were normal. Chest X-ray examinations showed nothing abnormal until May, 1943, when the signs of miliary tuberculosis were found. Intestinal obstruction developed. Laparotomy revealed a large retroperitoneal mass, consisting of caseating tuberculous mesenteric lymph nodes. The patient died a few days later. The autopsy showed generalized miliary tuberculosis. Retroperitoneally there was a doughy, semifluctuant mass, which contained multiple caseated areas. On microscopic examination the mass was composed of a fibrous tissue framework enclosing multiple small and large areas of necrosis. There was complete destruction of the lymphoid tissue and tubercle bacilli were seen. Symptoms similar to sprue occur in obstruction of the lymphatic vessels due to various chronic inflammatory diseases of the mesenteric lymph nodes.—*Intestinal Malabsorption Associated with Tuberculosis of Mesenteric Lymph Nodes*, A. Klein & W. B. Porter, *Arch. Int. Med.*, August, 1944, 74: 120.—(G. C. Leiner)

**Tomography in Bone Tuberculosis.**—This method of X-ray examination is a valuable addition to the diagnostic possibilities of the conventional X-ray films in bone tuberculosis. A positive diagnosis can be made sooner, the exact extent of the lesion can be better seen and treatment can be evaluated more readily. The fine structure of bone is not as easily recognizable as in the ordinary X-ray film due to the movement of the tube, and therefore tomograms of bone will not replace the conventional plates, but merely add information to their interpretation. The technique is also useful for dense bones, such as hip, spine and knee. In diagnosis of tuberculosis of the spine, frontal planes are more useful than

lateral ones. Case reports show that the early spinal lesion is not in the anterior part of the vertebra, as was formerly believed, but it starts in the central or posterior portion of the body of the vertebra. Neither is narrowing of the intervertebral space an early sign of bone tuberculosis.—*Beitrag zur Tomographie der Knochen und Gelenke unter besonderer Berücksichtigung der Knochen und Gelenktuberkulose*, E. Mordasini, *Schweiz. med. Wchnschr.*, February 5, 1944, 74: 123.—(H. Marcus)

**Tuberculosis of Hip.**—Successful treatment of tuberculosis of the hip requires from four to five years. Sunlight at high altitudes or sunlight in combination with sea climate affects the disease favorably, and sanatoria built in such locations can report the best results. Conservative treatment in such institutions heals approximately 60 per cent of tuberculous hips. The remaining 40 per cent develop abscesses and fistulae or become crippled as a result of pseudo-arthroses, subluxations and permanent shortening. These cases are better treated by operation in the second or third year of the disease. If isolated foci are present, the treatment of choice is resection, as is possible with lesions in the greater trochanter, the acetabular rim or the femoral neck. Resection of the hip joint itself is not successful because the disease usually progresses. The ideal treatment in these cases is extraarticular arthrodesis with fixation in optimal position. To this end a piece of bone with periosteum is chiseled out of the ileum about 1 cm. below the ileac crest. It is left attached at the base and is bent over and attached to the greater trochanter which has been incised for the purpose. This bony graft forms a bridge from the ileum to the trochanter and results in a firm arthrodesis. The end results are good in children and in adults. Healing of the involved hip joint proceeds rapidly, pain disappears, fistulae disappear and a firm extraarticular joint results which permits weight-bearing without pain and without more deformity than a slight limp.—*Unsere Erfahrungen mit der extra-fokalen Arthrodese der Hüftgelenktuberkulose*

beim Kinde und beim Erwachsenen, A. D. Chakar, *Schweiz. med. Wchnschr.*, April 8, 1944, 74: 371.—(H. Marcus)

Levinson and Tryptophan Tests.—At the City Hospital, Cleveland, in studying 36 proved cases of tuberculous meningitis, the Levinson ratio was found to be positive in 50 per cent, negative in 44 per cent. The tryptophan test was positive for 21 per cent of 34 proved cases of tuberculous meningitis, but also positive for 11 per cent of patients ill with other diseases. The authors conclude that more patients ill with tuberculous meningitis than with any other disease show a positive Levinson ratio and a positive reaction to tryptophan, but neither of these two tests is pathognomonic.—*The Levinson Ratio and the Tryptophan Test: Comparative Value in the Diagnosis of Tuberculous Meningitis*, F. A. Kriete, H. C. Epstein & J. A. Toomey, *Am. J. Dis. Child.*, June, 1944, 67: 469.—(K. R. Boucot)

Tuberculosis of Thyroid Gland.—Two forms of tuberculous involvement of the thyroid gland have been described, miliary involvement in generalized miliary disease and tuberculous abscess. The latter type is frequently not diagnosed clinically since other evidences of tuberculosis in the body may be lacking. In a review of 25 cases reported in the literature, and one additional case reported in this communication, the author found only 9 cases showing evidence of tuberculosis elsewhere in the body. The most common symptom is swelling of the thyroid, occasionally in a pre-existing goitre. The other symptoms may be due to pressure by the enlarged gland on neighboring structures, such as on the recurrent laryngeal nerve. Differential diagnosis must include acute suppurative thyroiditis, nonsuppurative thyroiditis, hemorrhage into a cystic adenoma, malignant neoplasm, struma lymphomatosa, Riedel's struma, actinomycosis and gumma. The condition is treated by incision and drainage, with or without packing of the abscess cavity, or by excision. Post-operative sinuses may remain which heal eventually. The value of X-ray therapy or

ultraviolet radiation remains doubtful. Purulent mediastinitis is a rare and fatal complication following excision.—*Tuberculous Abscess of the Thyroid Gland*, R. W. Postlewhait & P. Berg, *Arch Surg.*, June, 1944, 48: 429.—(H. Marcus)

Hepatosplenomegaly and Tuberculous Polyserositis.—A case of primary hepatosplenomegaly with secondary tuberculous polyserositis is presented. Two distinct phases could be observed in the clinical picture of this patient: First there was a hepatosplenomegaly accompanied by fever and a hypochromic anemia with leucopenia and lymphocytosis. This stage lasted for eleven months and was then followed by exudative peritonitis and pleurisy of six months' duration. At autopsy there were caseous tuberculosis of some abdominal lymph nodes and toxic hepatitis with scattered fibrocaseous foci in the liver. The spleen showed caseous necrosis and sclerotic hyperplasia and small hemorrhagic foci. The author considers this a case of clinically primary tuberculosis of the liver and spleen, pathologically secondary to tuberculosis of abdominal lymph nodes, from which the extension had taken place via blood vessels rather than via the lymphatics.—*Epatosplenomegalia e poiserosite tuberculare*, A. Segal, *Riv. di pat. e. clin. d. tuberc.*, 1940, 14: 385.—(G. Simmons)

Pneumothorax at Altitude.—In accordance with Boyle's law a pneumothorax gases expand with increasing altitude. The authors therefore investigated human subjects with pneumothorax because of the importance of such behavior in air-transported casualties and they cite their results in 2 cases. X-ray films were taken at levels of 5,000 feet on standard size films; a Millikan oximeter attached to the patient's ear provided an estimation of the arterial blood oxygen; pulse and respiratory rates were recorded at 5,000-foot intervals; excess oxygen was given from ground level by standard B-L-B masks; ascent in a decompression chamber was made at the rate of 1,000 feet per minute. Of the 2 cases observed, one had a 20 per cent collapse and a

stable mediastinum, the other had a 50 per cent collapse and a movable mediastinum; they illustrated a marked difference in tolerance due to these factors. As greater altitudes were reached, the degree of collapse, pulse and respiratory rates increased while the oxygen percentage of the blood decreased. The patient with the smaller collapse was able to tolerate an altitude of 20,000 feet while the second patient felt most uncomfortable at 15,000 and compression was done at the rate of 2,000 feet per minute with rapid disappearance of symptoms. The authors conclude that (1) continued aspiration of the pleural cavity should be carried out in cases with bronchopleural fistula, (2) cases with sucking chest wounds should not be transported by air until the wounds have been prevented from sucking more air into the chest, (3) in cases of large pneumothorax, aspiration of air should be performed prior to the take-off, (4) flying altitude must be considered and (5) any distress from cough should be allayed. It is natural to assume that a small pneumothorax and a fixed mediastinum will probably give little discomfort even at 20,000 feet.—*Investigation of Pneumothorax and Respiratory Function at Altitude*, E. W. Peterson, B. S. Kent, H. R. Ripley & D. R. Murphy, *Canad. M. A. J.*, June, 1944, 50: 520.—(W. C. G. Munroe)

**Recurrence of Malaria after Institution of Pneumothorax.**—Recurrence of malaria shortly after the institution of a pneumothorax was observed in 2 cases of pulmonary tuberculosis. The malaria had been clinically silent for a long period and recurred in both cases within twenty-four hours after the induction of pneumothorax. The author believes that the lungs act as a filter for bacilli, as well as for parasites, and that microemboli, consisting of infected red blood cells, may be forced back into the general circulation following the institution of collapse therapy, thus causing an acute relapse of malaria.—*Recidiva malarica dopo l'istituzione di pneumothorace terapeutico*, B. Besta, *Riv. di fisiol.*, 1940, 13: 91.—(G. Simmons)

**Early Pneumonolysis.**—The data on nearly 8,000 cases of pneumonolysis are critically analyzed and evaluated. This series includes 55 cases done by the author, and over 2,000 cases collected by Moore in 1934. Thoracoscopy and pneumonolysis in suitable cases are an essential part of pneumothorax, a fact which some physicians forget. Indeed, it is impossible to assess the results in a pneumothorax series until it is known whether pneumonolysis has done or not, and whether it was complete or only partial. Of course, a concentrically free collapse should be the aim of all pneumothorax. In many cases the presence of adhesions or their operability can only be determined by a thoracoscopy which is harmless; the earlier this is done the better. In unsuitable cases the lung should be re-expanded and treated by some other method, usually thoracoplasty. The division of adhesions preventing satisfactory lung collapse results in improvement in the mechanical character of the collapse, and is the only direct result of the pneumonolysis, barring complications. The postoperative complications are also reviewed. Mortality from all causes was only 1 per cent, chiefly by lung trauma, infection and intrapleural hemorrhage. Trauma and infection are usually caused by defective judgment and failure to recognize inoperable adhesions. Hemorrhage generally is the result of accidental injury to a vessel. Adhesions, especially short ones, should not be divided, but rather released at the parietal end, or left alone. The incidence of complications is about equal with electrocautery or galvanocautery. Most surgeons still prefer the latter. Sputum conversion was obtained in 73 per cent of cases (average). These clinical results of improved collapse are attributed to the pneumothorax and are reported as such. The author makes a strong plea for thoracoscopy or pneumonolysis early in the course of a pneumothorax when collapse is not perfect or when sputum remains positive.—*Closed Intrapleural Pneumonolysis*, J. Goorwitch, *J. Thoracic Surg.*, June, 1944, 13: 233.—(W. M. G. Jones)

# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**A Pneumonolysis Sponge Carrier.**—A simple sponge carrier for intrathoracic work is described. It is rigid enough for use in the enucleation of adhesions. The gauze tape is threaded through an eye and the long end fixed on a prong at the handle. When soiled the gauze is released at the handle and merely pulled through the eye without rethreading. It is made by the American Cystoscope Makers, New York.—*A Pneumonolysis Sponge Carrier and Dissector, J. S. Conant, J. Thoracic Surg., June, 1944, 13: 267.*—(W. M. G. Jones)

**Hemorrhage from Subclavian Vein during Pneumonolysis.**—During closed internal pneumonolysis for an adhesion attached to the apex of the chest above the first rib, the subclavian vein was entered and a large hemorrhage ensued. The only sterile instrument at hand was a scalpel. Iodine was hastily and liberally applied and the chest opened widely in the fourth interspace without benefit of any anesthetic. Only sterile towels were at hand and these were used to stop the hemorrhage by packing them into the apex. Only five minutes elapsed from moment of hemorrhage to its control. The wound was left open and patient returned to his ward. No blood or plasma was available but patient survived following intravenous fluids. Later gauze rolls were substituted for the pack of towels. About 1,200 cc. blood was removed from the chest, which was then closed. Two days later chest was reopened and gauze pack removed. Patient developed an empyema which healed following drainage. Eventual

death from spread of disease to good lung occurred five years later.—*Serious Hemorrhage during Closed Internal Pneumonolysis, R. A. S. Cory, J. Thoracic Surg., February, 1944, 13: 32.*—(W. M. G. Jones)

**Apicolysis with Extrapleural Pneumothorax.**—Apicolysis with an extrapleural pneumothorax is being performed in the Sanatorium "Principi di Piemonte" rather frequently and in preference to thoracoplasty because the operative trauma of the former is smaller, there is no resultant deformity and it is assumed that the respiratory function of the collapsed lung may be restored after reexpansion. Complications are numerous and results dubious in many cases. The author insists, however, that excellent results can be obtained if clinical indications for this operation are strictly adhered to. Apicolysis may be performed in patients whose general condition is worse than would be required before a thoracoplasty, and in the presence of contralateral disease, as long as the latter is not active. The disease on the side to be operated on must be stationary or only slowly progressive and the cardio-respiratory function tests must be satisfactory. Great importance in the problem of the indication is being attached to the site, size and structure of cavities to be collapsed. Thick-walled cavities and those located below the sixth rib must be excluded as well as cavities whose diameter exceeds 4 to 5 cm. It is agreed that many of the cases presented could have been treated equally successfully with a thoracoplasty and that, on the other hand, the apicolysis as advocated



cannot take the place of thoracoplasty in the treatment of pulmonary tuberculosis.—*Alcune considerazioni sulle indicazioni cliniche dell'apicolisi con pnx extrapleurico chirurgico nella terapia della tubercolosi polmonare*, A. Omodei-Zorini, *Minerva med.*, 1943, 34: no. 1.—(G. Simmons)

**Extrapleural Pneumothorax.**—The operative technique described here is essentially that of Schmidt. The operation is performed under local anesthesia with the patient in a sitting position. About 3 inches of the third rib are taken out posteriorly, following which the parietal pleura is separated from the endothoracic fascia under direct illumination. Since the lung has a tendency to reexpand, the pneumothorax space must initially be considerably greater than would appear necessary, according to the location of the lesion. Rivanol (150 to 220 cc.) is introduced into the space, for the antiseptic and hemostatic properties ascribed to this substance, and left there for about five minutes. There is always fever following the operation and a small amount of blood accumulates in the space. Refills are being given at four- to five-day intervals for the first two months and at greater intervals later on; the amount of air introduced is about 100 cc.; pressures obtained are as high as +60. Complications are mainly postoperative hemorrhage, suppuration and lung perforations; they are rather frequent. One hundred and twenty cases are presented, divided in two groups. The first group was operated on according to Schmidt's technique, the second according to the author's modified technique and postoperative treatment. In 81 patients sputum conversion was achieved; 18 patients died. Six cases, accompanied by roentgenograms, are described in detail.—*L'apicolisi con pneumotorace extrapleurico*, P. Abruzzini, *Minerva med.*, 1943, 34: no. 1.—(G. Simmons)

**Extrapleural Pneumothorax.**—A case of an extrapleural pneumothorax was accidentally discovered at autopsy. Air was trapped in a pathological space formed within the parietal

pleura on the left. Histological examination disproved the possibility that the outer wall of this pocket may have been formed by fibrin, organized after the absorption of a pleurisy with effusion which had occurred during collapse therapy. Both walls of the pocket proved to be formed by layers of the parietal pleura. Microscopic examination furthermore proved that the tear in the parietal pleura had occurred between the epipleura and mesopleura.—*Un raro caso di pneumotorace extrapleurico*, Bottero, *Arch. di med. e chir.*, 1939, no. 5.—(G. Simmons)

**Diaphragmatic Pain in Postoperative Hemorrhage.**—Six out of 53 cases of apicolysis with institution of an extrapleural pneumothorax developed severe postoperative hemorrhage six to twenty-four hours after the operation and one patient died of this complication. This complication is always accompanied by a severe pain over the operated side and is preceded by the pain, which must be considered an important signal of alarm.—*Sul dolore diaframmatico, segno di allarme nella emorragia post-operatoria da pnx. extrapleurico chirurgico*, P. Abruzzini, *Lotta contro la tuberc.*, 1940, 11: no. 12.—(G. Simmons)

**Phrenic Paralysis.**—The indications for phrenic paralysis are still ill defined. As an ancillary form of collapse in partial pneumothorax its value is well established, but it is seldom used as a first-line treatment, and by few in early cases. In an attempt to assess its value in early cases, 265 consecutive operations have been reviewed and the results of operation in 145 early cases have been classified. The following were the indications for operation for the entire group: (1) for the control of hemoptysis — 3 cases; (2) for the relief of pain — 4 cases; (3) for the consolidation of improvement already gained by sanatorium treatment — 18 cases; (4) as a palliative treatment in advanced disease — 30 cases; (5) as an ancillary treatment to pneumothorax — 64 cases; (6) in "suitable" early lesions when it was either the treatment of choice or followed the failure to induce

pneumothorax — 145 cases. The final classification was made on discharge from sanatorium, and a "successful" result was one in which the sputum was negative, the cavity, if previously visible, could not be demonstrated, and the area of infiltration was reduced and had the appearance of healing disease. The results of 145 consecutive operations for phrenic paralysis as a primary treatment in early lesions revealed successful results in 58 per cent of cases in which less than half of one lung was involved and in which the cavity did not exceed  $1\frac{1}{2}$  inches in diameter. The author advocates temporary phrenic paralysis as a primary treatment in early lesions of limited extent, and it can be made permanent if necessary.—*Phrenic Paralysis: Its Place and Value in the Treatment of Tuberculosis*, F. L. Wollaston, *Tubercle*, July, 1943, 24: 121.—(E. H. Rubin)

**Phrenic Paralysis.**—The value of alcohol injections into the phrenic nerve as a means of producing paralysis lasting (three months to three years) in those cases in which a temporary result only is desired is stressed. Twenty cases were thus injected out of a total of 1,000 operations for phrenic paralysis and the results were satisfactory.—*Per una estensione delle indicazioni della paralisi diaframmatica*, A. Bruscia, *Riv. di tisiol.*, 1940, 13: 150.—(G. Simmons)

**Pneumoperitoneum.**—The main indications for pneumoperitoneum are: (1) bilateral tuberculosis in which pneumothorax and phrenic paralysis have been unsuccessful or not feasible; (2) uncontrolled hemorrhage; (3) additional treatment after abandonment of pneumothorax; (4) supplementary therapy to phrenic paralysis. The changes produced by pneumoperitoneum consist of lymph stasis and subsequent fibrosis, pulmonary anoxemia, reduction in chest capacity, relaxation of tissues and diminution of toxic signs and symptoms. Among the advantages of this method of treatment are its reversibility and the fact that the reduction in vital capacity occurs but gradually. Complications (air em-

bolism, ascites, mediastinal emphysema, etc.) and contraindications (fixed diaphragm on the diseased side, coronary and generalized arteriosclerosis, amyloidosis, etc.) of pneumoperitoneum are then enumerated and the authors' technique described. At autopsy inflammatory changes of the peritoneum have been observed in only 10 per cent of cases. Electrocardiographic changes during pneumoperitoneum consist of shift of the electrical axis to the left in the absence of diaphragmatic paralysis, and shift to the right or to the left in the presence of right or left phrenic paralysis, respectively. The case of a twenty-six year old female, with a subclavicular cavity on the left and infiltrations in the right upper lobe is described. After left pneumothorax and left phrenic crush had been unsuccessful, pneumoperitoneum was induced and maintained for two years, with resulting closure of the cavity and sputum conversion. Pneumoperitoneum can be used to good advantage in selected cases.—*Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis*, B. M. Stuart, R. L. Pullen & J. L. Wilson, *New Orleans M. & S. J.*, August, 1944, 97: 61.—(P. Lowy)

**Pneumoperitoneum.**—The aim of the article is to show that pneumoperitoneum has a place in the collapse therapy of pulmonary tuberculosis. What this place is has not been sufficiently defined. The treatment cannot be regarded as a substitute for other forms of collapse therapy but rather as an additional measure likely to prove valuable in particular cases. Pneumoperitoneum is essentially an interim measure directed specifically to achieving cavity closure, usually in association with other forms of collapse therapy, especially phrenic crush and artificial pneumothorax. As to the length of time a pneumoperitoneum should be maintained, the general rule appears to be that it is a matter of months only, although there are exceptions. The best results are obtained when disease affects mainly the lower zones. The major complications are perforation of the bowel, air embolism, intra-peritoneal effusion, accidental pneumothorax,

mediastinal emphysema and cardiac decompensation. Details of 10 illustrative cases are given.—*Pneumoperitoneum in the Collapse Therapy of Pulmonary Tuberculosis*, E. Clifford-Jones & N. Macdonald, *Tubercle*, June, 1943, 24: 97.—(E. H. Rubin)

**Thoracoplasty through Small Muscle-splitting Incisions.**—At the Philadelphia General Hospital the author has revived an old operation first described by Head, 1928; and again by Head and by Wangenstein in 1938. Instead of using the conventional scapula-mobilizing hockey-stick incision, this procedure employs four to six small muscle-splitting incisions, three of these posterior and three anterior. Through each incision long segments of two to three ribs can be resected with ease. The authors, however, employ special long periosteal rib strippers, which can be used to advantage where the exposure is limited. An apicolysis may be done if desired through the upper posterior incision. As each stage is small, shock is minimal or absent; indeed the author claims the patient is often "able to feed and bathe himself the day following operation and on the second day may even walk to the bathroom." The economy in nursing care is therefore great. Functional and cosmetic results are also better than with the conventional incision. At first the operation was used only for the very sick or mixed infection empyemata, but is now used routinely for all cases. Both the medical staff and the patients appreciate the smaller operation and take it more willingly.—*Muscle-Splitting Thoracoplasty*, R. M. Lewis, *J. Thoracic Surg.*, October, 1944, 13: 431.—(W. M. G. Jones)

**New Treatment of Residual Cavities.**—Here is a new treatment for an old problem, the residual cavity after thoracoplasty. That this procedure is effective is shown by the report that 22 of 23 cases so treated now have complete sputum conversion. There were no deaths and no serious complications. The claim is made that the lung mobilization does not increase surgical shock and very greatly

lessens the paradoxical motion of the chest wall so common after extensive revisions. The author discusses the essential principles to be followed to give satisfactory collapse of the lung in the first series of thoracoplasty operations, namely: (1) the resection of transverse spinal processes and sufficient lengths of the necessary number of ribs; long anterior rib segments are not permitted; (2) the application of 10 per cent formalin to periosteal rib beds, especially the upper three; (3) elimination of undue delays between stages; the optimum interval is three weeks; (4) maintenance of an adequate period, seven months or more, of strict bed-rest following completion of the surgical program. The Semb procedure of apicolysis has advantages, especially for large upper lobe cavities, but the dangers of this mediastinal dissection (chiefly infection) seem to outweigh the advantages, and it has been abandoned. Despite all these measures and precautions, certain cases continue to have persistent cavity and positive sputum. During the past three years (1941-1944) these authors have had 203 cases come to thoracoplasty; and another 39 have had to have revision operations for residual cavities. Of these 39, 23 have had "mobilization and fixation" as described herein. The various methods of treating these residual cavities are discussed, but none of them have given satisfactory results to secure general adoption. The list of these is quite large: apicolysis (Semb and Overholt), myoplastic thoracoplasty (Head), pneumonectomy or lobectomy (Dolley and Jones, Alexander), pedicled muscle flaps (Coryllos and Ornstein), extrapleural gauze packs, intracavitary drainage (Mondaldi), flap drainage (Rogers). The method proposed here sacrifices as little lung tissue as possible, has few complications, and gives a smooth convalescence along with a high percentage of cavity closure. The procedure is as follows: Following the usual revision operation the lung is mobilized posteriorly by incising scar tissue along the spine and, by blunt dissection, the lung is freed and elevated out of the posterior vertebral gutter and from the lateral aspects of the vertebral bodies. The

intercostal bundles are dissected forward and their posterior portions freed as far as necessary (by dividing external intercostal muscles only the intercostal structures as a whole are carried along with the lung). Blood supply to the lung is thus maintained. On the anterior aspect of the vertebral bodies care must be exercised to preserve the sympathetic trunk, thoracic duct, etc., but these structures need not be exposed. The dissection is carried upward to the second dorsal vertebra and downward to the vertebral body of the last rib resected. (The authors have not carried this dissection below the eighth rib.) The lung thus mobilized is then rolled forward and sutured in position with black silk and No. 2 chromic catgut doubled. The sutures are passed through the dense fibrous tissue overlying the lung mass posteriorly and through the similar fibrous mass anteriorly or through the cartilagenous chondrosternal portion of the resected ribs. The wound is closed in layers without drainage. This operation should not be performed at the time of the primary thoracoplasty because of the absence of scar tissue suitable for suturing. Moreover it cannot be used in empyemal cases. Postoperatively as soon as tolerated, sandbags, shotbags and wedge pillows are used. One case required aspiration of fluid by needle. There were no infections. The author recommends this procedure for routine use with any revision thoracoplasty to close a residual cavity.—*Surgical Management of Residual Tuberculous Cavities following Primary Thoracoplasty*, A. R. Judd, *J. Thoracic Surg.*, June, 1944, 13: 249.—(W. M. G. Jones)

**Thoracoplasty Results.**—The clinical material that forms the object of this review includes cases with good, fair and poor indications. The indication in this latter group seemed to be justified in spite of the unfavorable circumstances by a certain percentage of success in a group of cases otherwise doomed. The operation was always preceded by a complete study of the patient, including laboratory investigations, complete X-ray studies and bronchoscopy. Local infiltration

anesthesia with 0.5 per cent novocaine was used with or without epinephrine; in some cases Evipan was used to complement the anesthesia. In the five years previous to this publication, 8,000 patients were admitted, 457 (5.7 per cent) of whom were considered for thoracoplasty. The indication was accepted and the operation performed in only 200 cases. Twenty-nine cases presented good indication (14.5 per cent), 48 cases fair and 123 poor indication, (24 per cent and 62.5 per cent, respectively). The percentage of mortality was as follows: 10 per cent in the first group, 33.3 per cent in the second and 35.7 per cent in the third group. One hundred and thirteen of the operated patients were males and 87 females. The great majority of the patients belonged to the age groups between twenty and thirty-four years. The oldest patient operated on was fifty-nine years old. In the age groups above forty years a marked rise in the mortality rate was observed. The operation was performed more frequently on the right side. Short intervals between the stages of the operation proved to be advantageous; longer intervals were motivated by various causes, such as infection of the wound in over 50 per cent of the cases. The frequent occurrence of wound infection is explained by the poor general status of the patient, by pleural suppurations affecting the peripleural tissues, by the infection of an extrapleural hematoma and by exogenous infection. The local use of sulfanilamide may reduce the incidence of wound infection. Ninety per cent of the patients had far advanced lesions; only 10 per cent had moderately advanced lesions; all of them showed evidence of cavitation. Thirty-eight cases (19 per cent) were apparently cured by the intervention; in 43 cases (21.5 per cent) the thoracoplasty was followed by improvement; in 56 cases there was no improvement and 63 patients were dead at the time of this publication. In the evaluation of these poor results, the authors emphasize that they were led in their indications more by the purpose of saving human lives than by their desire to publish brilliant statistics. The presence of pneumothorax

either on the operated side or on the opposite side has impaired their results. Poor therapeutic effects were obtained also in cases with giant cavities, that is, cavities having a diameter of over 4 cm. Fibrous lesions in the opposite lung were the least affected by the thoracoplasty, while fibro-ulcerative and exudative processes in the contralateral lung had an unfavorable effect on the results. Tuberculous empyemata associated with parenchymatous lesions and those with mixed infection, especially if operated at a late stage of the disease, gave a high mortality rate. The conversion of the sputum occurred in 69 cases out of 137 who were alive at the time of this communication. The persistence of positive sputum in patients with apparently good collapse of the diseased area is explained by the presence of tracheobronchial lesions.—*Revisión estadística y estudio clínico de 200 casos de toracoplastia operados en el Hospital-Sanatorio "La Esperanza," C. V. Figueral, L. C. Lopez, J. D. Garteiz & M. B. Bravo, Rev. de tuberc. (Habana), January-March, 1944, 1: 29.*—(L. Molnar)

**Late Results of Thoracoplasty.**—This study gives a 100 per cent follow-up of 232 cases of thoracoplasty for the ten years, 1931 to 1941, at the Koch Hospital (St. Louis Municipal Sanatorium). About one-third of the patients were Negro. Ineffective pneumothorax was abandoned in 90.5 per cent, and hence only 6 per cent (13 cases) had empyema. Tracheobronchial disease was first treated bronchoscopically. There were bilateral cavities in only 8.4 per cent (19 cases), and in these the disease on the good side was controlled by pneumothorax, phrenic crush or pneumoperitoneum. Eighty-two patients had phrenic crush. The cases are presented in three groups of about equal size, each representing different surgical techniques and criteria for the years 1931-1935, 1936-1938, 1939-1941. The improvement in these factors is reflected in the reduced number of revisions necessary (6 and 2 in the latter periods as compared to 42 in the former); in the lowered over-all six-year mortality (24.5 and 20.2 per cent as com-

pared with 35.8 per cent); the improvement in over-all favorable results (74.0 and 78.7 per cent as compared to 49.7 per cent for the older group); and the reduction in hospital stay (3.0 and 2.3 years instead of 4.7 years). The one-year operative mortality for the whole 232 cases was only 4.7 per cent.—*Thoracoplasty for Tuberculosis, A. R. Valle, J. Thoracic Surg., February, 1944, 13: 36.*—(W. M. G. Jones)

**Physical Findings after Thoracoplasty.**—For the diagnosis of residual cavities after thoracoplasty, overexposed films and tomograms are extremely valuable. The author has correlated the physical and radiographic findings in 11 operated cases. Tuberculous infiltrations cannot, as a rule, be recognized on physical examination following thoracoplasty, but cavities of moderate and large size can be picked up with the stethoscope. On percussion, moderate to marked dullness is the rule, depending on the type of operation performed. Areas of tympany are discovered to lie over relaxed normal lung tissue. These areas are frequently found beneath the clavicle. Tympany is rarely obtained over a cavity. On auscultation a great many adventitious sounds are heard and it is advantageous to examine the patient while he is breathing quietly. This minimizes the number of râles due to mechanical compression and kinking of the bronchi. With quiet respiration, resonating râles are due to cavity formation. Physical examination is, of course, not advocated in place of X-ray films and tomograms to determine residual cavities, but as a guide to such procedures to avoid excessive cost of X-ray examinations. Before each case is finally evaluated and treatment decided upon, sputum examinations and a thorough check-up of the other side are in order.—*Klinischer und radiographischer Befund bei Thorakoplastik, R. Banderet, Schweiz. med. Wchnschr., March 25, 1944, 74: 310.*—(H. Marcus)

**Wound Infection in Thoracoplasty.**—At the Robert Koch Hospital there were 339 thoraco-

plasties performed in two and one-half years prior to July, 1942. Of these, 11.8 per cent showed infection of the operative wound. Drainage of the wound was employed 52 times. The causes of wound infection were investigated and a second series of 120 operations was carried out without a single infection of any kind. None of this series was drained. The precautionary measures are discussed as follows: (1) the elimination of contamination from skin and air, (2) the operative technique, (3) the postoperative care of the wound and (4) the general treatment of the patient. The routine procedure is as follows: The skin is scrubbed repeatedly with soap and water, starting several days before the operation. In the operating room the skin is treated with ether, 3.5 per cent tincture iodine and then alcohol. After the incision is made the skin is covered with thick absorbent pads (to absorb blood or perspiration) under the usual sterile towels applied to the edges of the skin. The skin is treated with alcohol again before the skin is sutured. During the operation only the working area is allowed to be uncovered. Before closure the wound is thoroughly irrigated with saline solution. In the operative procedure there is gentleness and careful debridement of all loose soft tissue. Closure is effected with the smallest suture material, 0 chromic for the muscles, 000 chromic for fascia and A silk for the skin. Few bleeding vessels are tied, but all bleeding spots are included in the interrupted muscle suture. (Sanguinous fluid had to be aspirated 6 times.) Postoperatively a pressure dressing is used, employing mechanics "waste." Hematomata are aspirated only. Finally, to ensure rapid healing of the wound, a high protein diet with additional vitamins is used, both before and after surgery. Every case had a blood transfusion.—*The Problem of Wound Infection in Thoracoplasty*, Y. K. Wu & M. B. Planetto, *J. Thoracic Surg.*, October, 1943, 12: 648.—(W. M. G. Jones)

**Wound Infection in Thoracoplasty.**—Two series of thoracoplasty operations are presented to show the beneficial effect of dusting

5 g. of sulfathiazole into the wound before closure. In the first series there were 90 operations with 69 per cent primary healing, 17 per cent of superficial sepsis and 5 per cent of deep sepsis. In the second series, performed under more or less identical conditions, the use of the sulfathiazole in 90 stages gave 93 per cent of primary healing and no cases of superficial or deep sepsis. Most patients were colored Jamaicans. The wound was not washed with saline. Formalin was used routinely for the periosteum. Toxic effects of the drug were not seen in any case.—*Wound Healing after Thoracoplasty in a Tropical Hospital*, R. A. S. Cory, *J. Thoracic Surg.*, October, 1943, 12: 653.—(W. M. G. Jones)

**Cavity Drainage.**—From experiences collected to date, the place of cavity drainage in the treatment of tuberculosis can be more or less exactly defined. After pneumothorax therapy has been unsuccessful in certain cases, the chances for a success of endocavitary drainage are good. Such cases are large cavities which show no tendency to collapse in spite of a technically good pneumothorax, frank tension cavities, lower lobe cavities or upper lobe cavities suspended by uncuttable adhesions. Cavity drainage has also widened the indications for phrenic crush. A combination of these two procedures is especially useful in cavities of the middle and lower lung fields, cavities in the apex of the lower lobe, centrally located cavities (if the proximity to large blood vessels can be excluded) and in upper lobe cavities when for some reason thoracoplasty is not under consideration. The procedure is also advocated in combination with thoracoplasty, especially when multiple cavities are present, or if the cavity is larger than one can expect to close by thoracoplasty. Also, in patients in poor general condition, preoperative cavity drainage helps to improve the patients' status so that they can be operated on at a later date. The procedure also has a place in the treatment of residual cavities after thoracoplasty. In the latter type of case it carries practically no risk. The results of cavity drainage are better

in unilateral disease than in bilateral and in this respect it does not differ from the usual methods of collapse therapy.—*Kavernensaug-drainage und kollapstherapeutische Indikation bei Lungentuberkulose*, St. J. Leitner, Schweiz. med. Wchnschr., April 8, 1944, 74: 369.—(H. Marcus)

**Physiological Approach to Pulmonary Resection.**—The newer operative techniques no longer make it necessary to sacrifice a whole lobe or lung in performing resection of pulmonary tissue. New advances in anesthesia and the technique of individual ligation allow more time at the operation and result in many fewer cases of putrid empyema. A new physiological concept is presented—that of considering the surgical units of the lungs as the bronchopulmonary segments, rather than the better defined lobes. Thus, there are eight surgical lobes, each with its own bronchus, arterial and nervous channels accessible for individual ligation. These are the two upper, two middle (the lingula is comparable in every respect to the right middle lobe), and four lower lobes (each anatomical lower lobe is divisible surgically into a dorsal division and a basal division). These are well defined and constant and pathologically as well as surgically are of practical importance. For example, the dorsal divisions of the lower lobes are the most frequent site of abscess, but rarely the site of bronchiectasis which predominates in the basal segments. The upper lobes and the basal divisions of the lower lobes are each further divisible into four segments. The lingula and right middle lobe are likewise further divided into two segments each. Segmental pneumonectomy of any of these divisions is practicable and safe—except of the right middle lobe, where the two segments are indistinct and very little lung tissue would be saved anyway. Thus in many cases of bronchiectasis partial lobectomy would afford conservation of lung tissue hitherto not attainable. In peripheral tumors, likewise, segmental resection is often done until microscopic studies are completed, before the more radical pneumonectomy is

performed. In the author's 8 cases, there were no deaths and only one postoperative empyema. Accurate localization of the diseased segments and careful operative technique are stressed.—*Conservation of Lung Tissue by Partial Lobectomy*, B. Blades, Ann. Surg., September, 1943, 118: 353.—(D. J. Rednor)

**Pneumonectomy for Pulmonary Tuberculosis.**—From 1880 to 1942, 34 cases of lobectomy and 30 of pneumonectomy for tuberculosis are culled from the literature. Of these, 31 are known to be living and 29 reported dead. While indications for excision of lung tissue for tuberculosis have varied, the concensus is that bronchial stenosis is the strongest indication for operation. Blocked cavities and the failure of collapse therapy are also indications. Bronchial lesions should be quiescent, and the good contralateral lung absolutely free from disease. The case reported here was a nurse, age forty-five, who had left bronchial stenosis 2 cm. from the carina, atelectasis of the base and cavities in the upper lobe. Her vital capacity was 75 per cent of normal. Pneumonectomy was by hilar dissection method. Adhesions separated readily. The patient had absolutely no reaction to the operation and was in good health eighteen months later.—*Total Pneumonectomy for Pulmonary Tuberculosis*, M. Behrend, J. Thoracic Surg., June, 1943, 12: 484.—(W. M. G. Jones)

**Arterial Oxygen Saturation after Pulmonary Resection.**—Several hundred determinations of the arterial oxygen saturation in the post-operative period were made by the method of VanSlyke and Neill. The normal range is given at 94 to 96 per cent and as low as 92 per cent in older patients. Less than 90 per cent saturation is considered significant, and less than 85 per cent is considered as severe anoxia. Seventeen patients were studied following pneumonectomy—the majority had only slight reduction for the first week; in 2 cases there was prolonged unsaturation, associated with mediastinal deviation. Twenty-one cases were presented following

lobectomy. The return to a normal oxygen saturation level was slower than in the uncomplicated pneumonectomy cases. Most cases showed some anoxia in the first week. In most of the cases with abnormally low saturation for more than a week postoperatively, some interference with pulmonary ventilation was present—such as difficulty with reexpansion of a lobe, pleural fluid, atelectasis and pneumonic infiltration due to retention of bronchial secretions, diminished respiratory excursion, mediastinal displacement, emphysema and fibrosis, bronchial fistula. Five cases were presented following exploratory operations—all showed slight reduction varying from 89.5 to 93 per cent. Twenty-seven patients following thoracoplasty were investigated. A slight reduction was observed even in some good-risk patients without complications, and the majority showed an appreciable drop. As a control, 13 patients were studied following major abdominal surgery—no instance of anoxic anoxia was found. The authors emphasize that it is customary to administer oxygen for only a few days following operation unless cyanosis or dyspnea is present. Their studies show that a significant degree of anoxic anoxia persisted for weeks without dyspnea or cyanosis, and marked clinical benefit was derived when oxygen therapy was again instituted. Symptoms which suggest subclinical anoxia are headaches, restlessness and mental confusion. They believe unrecognized anoxia is common in thoracic surgery and prefer to make routine determinations of the arterial oxygen saturation so that anoxia will be detected in its earliest stages. They stress the greater unsaturation following lobectomy as compared with pneumonectomy and the increase in unsaturation following both procedures when complications are present. In the latter instance especially, prolonged oxygen therapy is recommended.—*Studies of the Arterial Oxygen Saturation in the Postoperative Period after Pulmonary Resection, H. C. Maier & A. Cournand, Surgery, February, 1943, 13: 199.*—(D. J. Rednor)

**Mediastinal Displacement following Pneumonectomy.**—Any displacement of the mediastinum, however slight, following total pneumonectomy can upset the cardiopulmonary function and result in grave consequences, if not corrected. Displacement toward, or away from, the operated side is of equal importance. The chief causes of displacement toward the contralateral side are (1) pleural fluid, (2) pneumothorax (especially tension type) and (3) atelectasis of the contralateral lung due to retained bronchial secretions. The causative factor if displacement toward the operated side is loss of pleural air by (1) subcutaneous emphysema, as in the anterior surgical approach where good closure of the intercostal muscles cannot be obtained or by (2) closed drainage of the water-seal type for infection, which results in an increasingly negative intrapleural pressure. The position of the mediastinum is best determined by serial postoperative X-ray films and intrapleural manometric readings. Increased pressure with displacement away from the operated side is treated by air or fluid aspirations or both, as necessary. Prevention and treatment of atelectasis of the contralateral lung must also be done. Decreased intrapleural pressure is best treated by giving small pneumothorax refills. The optimum final pressures should be neutral or slightly subatmospheric. A change in the position of the mediastinum can also occur without the mechanical alterations described above. For example, a shift toward the side operated on may occur, due to emphysema and hyperinflation of the remaining lung or due merely to the high negative pressure in the pleural space from which the lung was removed. Likewise, certain factors at operation can influence the position of the mediastinum in the opposite direction: namely, the lateral position of the patient on the operating table, a high amplitude of respiratory excursion when the thorax is being closed, and the sucking-wound action of the incision when it is almost closed, resulting in the tension-type pneumothorax. The importance of minimizing the degree of mediastinal displacement, from whatever cause, in the early



postoperative period, especially in the elderly and poor-risk group of patients is stressed. Pressure readings at the conclusion of the operation and at intervals thereafter, and roentgenograms on the first or second postoperative day and then at intervals of a few days are the surest diagnostic methods, if instances of cardiac irregularity and cardiopulmonary failure are to be successfully overcome.—*Cardiopulmonary Disturbances Associated with Mediastinal Displacement after Pneumonectomy*, H. C. Maier, *Surgery*, March, 1944, 15: 432.—(D. J. Rednor)

**Hypoproteinemia following Thoracic Surgery.**—Studies of the plasma protein level were done before and after 32 major chest operations on 29 patients. In 31 of these a drop was seen. The average decrease was 1.11 g. per cent in 14 lobectomies, 0.95 g. per cent in 5 pneumonectomies, in all cases about 1.0 g. per cent. The fall usually occurred from three to five days following operation and was accompanied by a similar decrease in hematocrit, hemoglobin and red blood cells. The principal causes of the drop in plasma protein were: (a) diminished protein reserve, (b) operative blood loss, (c) loss of blood and plasma into the wound and pleural space after operation, (d) infection, (e) inadequate replacement. Massive transfusion of whole blood was the most satisfactory single therapeutic agent when the plasma proteins were lowered due to hemorrhage.—*Hypoproteinemia in Thoracic Surgery: A Clinical Study*, T. F. Thornton, W. E. Adams & P. W. Schafer, *Surg., Gynec. & Obst.*, October, 1944, 79: 368.—(G. C. Leiner)

**Electric Charge of Bacteria.**—The filtrability of bacteria is determined by their electric charge, as was indicated in a previous paper by the author. The R type is predominant in the culture of tubercle bacilli and since it is, supposedly, charged positively, it would be retained by the filtre having a negative electric charge. The filtrable portion of a culture would have a different electric charge. Recent experimental studies

have demonstrated that the phenomena observed after the inoculation of S type of tubercle bacillus cultures are identical with those produced by the "ultravirus." It is more proper, therefore, to speak of filtrable forms of tubercle bacilli than of ultravirus. Experiments with cultures of *Pseudomonas aeruginosa* have confirmed this observation. The different electric charges would correspond to different morphological characteristics. The normal cultures contain germs of opposite electric charge, while the R and S types of cultures would represent different phases of dissociation of the culture.—*La carga electrica de las bacterias, factor determinante de su filtrabilidad y de la morfologia de las colonias*, R. C. Reig, *Publ. d. Inst. Antituberc.* "Francisco Moragas," Barcelona, 1943, 5: 83.—(L. Molnar)

**Bacteriostatic Chemicals for Tubercle Bacillus.**—The bacteriostatic effect of various chemotherapeutic and chemical substances, such as promanide, sulphanilamide, sulphathiazole, sulphadiazine, cetavlon, phemeride and potassium tellurite, on the growth of tubercle bacilli was determined. The author used the slide method described by Pryce where tubercle bacilli are grown on microslide preparations of sputum. The slide preparations were placed in medium containing the substance under investigation and incubated at 37°C. for seven days. The routine medium was made by mixing one part human citrated blood with two parts sterile distilled water. To this medium varying concentrations of the chemotherapeutic and chemical substance were added. Of the sulphonamide drugs tested the author found very little effect with sulphanilamide while sulphathiazole showed good bacteriostasis in a concentration of 5 mg. per 100 cc. Promanide produces very slight inhibition of growth. The kationic detergents, cetavlon and phemeride, produced complete bacteriostasis in concentrations of 40 and 20 mg. per 100 cc., respectively. Potassium tellurite gave complete bacteriostasis in concentrations of 10 mg. per 100 cc.—*On the Use of a Modification of Pryce's Slide*

*Culture Method for the Estimation of the Bacteriostatic Power of Chemicals on the Tubercle Bacillus*, H. Muller, *J. Path. & Bact.*, July, 1944, 56: 429.—(H. J. Henderson)

**Lytic Action of *Bacillus subtilis* on Tubercle Bacilli.**—A motile, sporulated and gram-positive germ of atmospheric origin is described which was found as an accidental contaminant in cultures of the tubercle bacillus. Observation disclosed a lytic action on tubercle bacilli and also on the Souza Araujo strain of the leprosy bacillus. An effort is being made to extract by various processes the active bacteriostatic substances. Among those so far investigated, only the one called crude subtiline has shown, both *in vitro* and *in vivo*, a bacteriolytic and antagonistic effect on the tubercle bacillus. Subtiline has not shown any toxic effect when administered in therapeutic doses to guinea pigs or rabbits.—*Lytic Action of Bacillus subtilis on Mycobacterium tuberculosis*, M. F. Magarao, A. Arriagada-V. & S. Thales, *Rev. brasil. de med.*, July, 1944, p. 556.—(A. A. Moll)

**Growth of Tubercle Bacilli on Hyperglycemic Blood.**—Basing his experiments upon the work of other authors who found that addition of blood to a culture medium is favorable for the growth of tubercle bacilli, the author confirms this opinion and states that hyperglycemic blood is more favorable than normal blood. Since, however, there is no difference in promotion of growth between normal blood and blood to which glucose had been added, it is concluded that diabetic blood may contain another factor, favorable for the promotion of growth of tubercle bacilli.—*Sul potere favorente lo sviluppo dei batteri del sangue iperglicemico dei diabetici e dei diabetici tubercolari*, V. Agnello, *Riv. di fisiol.*, 1940, 13: 361.—(G. Simmons)

**Filtrability of Tubercle Bacilli.**—The author investigated the possibility of the existence of a form of *M. tuberculosis* capable of passing through gradocol membranes of known porosity size. Saline suspensions of *M. stercusis*

and the human and bovine types of *M. tuberculosis* were filtered through a series of collodion membranes of decreasing pore size. The presence or absence of viable elements in the filtrates was determined by cultural or biological methods. The methods employed were unable to detect viable elements in filtrates drawn through membranes of A.P.D. 0.7 U.—*The Filtration of Mycobacterium Tuberculosis and Mycobacterium Stercusis through Gradocol Membranes*, M. A. Soltys & A. W. Taylor, *J. Path. & Bact.*, April, 1944, 56: 178.—(H. J. Henderson)

**Tuberculostearic Acid.**—By means of X-ray diffraction studies of tuberculostearamide and of dl-10-methyl-stearamide, the conclusion was reached that the differences observed were consistent with the hypothesis that tuberculostearic acid, although showing no detectable optical rotation, is optically active. Stearic acid and tuberculostearamide molecules had similar orientations in the crystal. The results support the structure of d- or l-10-methylstearic acid proposed for tuberculostearic acid.—*Chemistry of the Lipids of Tuberculostearic Acid*, S. F. Velick, *J. Biol. Chem.*, July, 1944, 154: 497.—(F. B. Seibert)

**Lipids of Tubercle Bacilli.**—Total lipids of the bacilli (strain H37), cultivated on a modified Long synthetic medium in which dextrose replaced glycerol, amounted to 30.6 per cent, comparable to that found on the unmodified medium. The lipids contained no phosphatide and only an acetone-soluble fat and a low melting wax. The acetone-soluble fat on analysis was similar in composition to the fat elaborated on a glycerol-containing medium. It contained tuberculostearic acid, phthioic acid, the pigment phthiocol, no glycerol but a carbohydrate which could not be definitely identified. The wax fraction differed from the waxes isolated from the tubercle bacillus cultivated on a glycerol-containing medium in that no high melting wax could be found. The low melting wax, however, gave on analysis certain of the characteristic components of the tubercle bacillus wax, namely, mycolic

acid, the alcohol phthiocerol, dextro-rotatory fatty acids analogous to phthioic acid, and a polysaccharide that contained pentose.—*The Chemistry of the Lipids of Tubercle Bacilli. LXVII. The Lipids of the Human Tubercle Bacillus H-37 Cultivated on a Dextrose-containing Medium*, M. M. Creighton, L. H. Chang & R. J. Anderson, *J. Biol. Chem.*, August, 1944, 154: 569.—(F. B. Seibert)

**Lipids from Cell Residues from the Preparation of Tuberculin.**—The lipids contained in tubercle bacilli residues from the preparation of PPD were extracted and separated into phosphatide, low melting wax, acetone-soluble fat, chloroform-soluble wax, and firmly bound lipids. In solubility these lipids resemble analogous fractions previously isolated from tubercle bacilli, strain H37, but certain differences in chemical composition were observed, which must be due to the strain of bacillus used.—*The Chemistry of the Lipids of Tubercle Bacilli. LXVIII. The Lipids of Cell Residues from the Preparation of Tuberculin*, M. M. Creighton & R. J. Anderson, *J. Biol. Chem.*, August, 1944, 154: 581.—(F. B. Seibert)

**Acetone-soluble Fat of Cell Residues from the Preparation of Tuberculin.**—The acetone-soluble fat isolated from tubercle bacilli residues from the preparation of PPD was found to be similar to that found in the tubercle bacillus, strain H37, and consisted of fatty acid esters of the disaccharide trehalose. Among the cleavage products liberated on saponification were the pigment phthiocol and anisic acid. The liquid saturated fatty acids contained, in addition to tuberculostearic acid and phthioic acid, several other higher liquid saturated fatty acids.—*The Chemistry of the Lipids of Tubercle Bacilli. LXIX. The Composition of the Acetone-Soluble Fat of Cell Residues from the Preparation of Tuberculin*, C. O. Edens, M. M. Creighton & R. J. Anderson, *J. Biol. Chem.*, August, 1944, 154: 587.—(F. B. Seibert)

**BCG.**—The author, in collaboration with Sayé in Barcelona, has studied the late results of vaccination from the viewpoint of allergy. Of 58 vaccinated children with active tuberculosis the majority had been exposed to massive infection during the first months of life at a time when the immunization was not yet complete. These cases were compared with 14 cases that had been vaccinated and had not suffered infection and they all were negative. The results seem to point out that extensive allergy in the vaccinated is a demonstration of a virulent infection. The author accepts the original suggestion of Calmette and concludes that the attenuated allergy obtained by vaccination should be maintained by revaccination since apparently the BCG is eliminated or destroyed in the organism in a time varying with the animal species and the absorbed doses.—*Estado actual de la vacunacion anti-tuberculosa de Calmette-Guérin*, R. Shelton, *Rev. de tuberc. d. Cuba*, October-December, 1942, 6: 169.—(F. G. Kautz)

**Immunization with Vole Bacillus.**—The vole bacillus was isolated in England from a meadow mouse by Wells in 1937. This bacillus is an apparently stable, slow growing waxy mycobacterium, which is more pleomorphic in tissue than the human and bovine bacillus, but cannot be distinguished from them by serological absorption of agglutinins. From it a tuberculin can be produced which gives allergic skin reactions in animals infected with mammalian tubercle bacilli. The vole acid-fast bacillus does not appear to be an attenuated bovine, human or avian bacillus, nor a form of the murine or human leprosy bacillus. Its distinguishing characteristics seem to be fixed. This particular organism is apparently a third fixed type mammalian tubercle bacillus in addition to the human and bovine types. In some respects it may be a "link" between tubercle and leprosy mycobacteria. The vole bacillus is highly pathogenic only for the vole (meadow mouse). In this animal it produces a slowly progressive disease with subcutaneous lesions paramount

—like those of rat leprosy in some respects. The vole bacillus causes localized lesions in cattle, hamsters, guinea pigs, rabbits and white rats without progressive systemic disease, unless overwhelming doses are used. It is innocuous to fowl. The rabbit is somewhat protected from bovine tuberculosis by vaccination with the vole bacillus. There are, as yet, no published accounts of its pathogenicity for monkey or man. Unpublished work indicates that progressive vole bacillus infection in monkey and man is improbable. As a matter of fact, 1 mg. (moist weight) of viable vole bacilli administered subcutaneously and intravenously in the human has given no evidence that it will produce progressive disease. On account of its close similarity to the human tubercle bacillus and its lack of virulence, the authors have been using the vole bacillus as an immunizing agent for guinea pigs against human tubercle bacilli. The present paper is a further report on the degree of immunity to virulent human tubercle bacilli in guinea pigs vaccinated with viable and heat-killed vole acid-fast bacilli. For comparison, a comparable group of guinea pigs vaccinated with BCG was studied. One hundred and fifty-seven guinea pigs of approximately the same age and weight were divided into four groups. Group I (43 animals) were vaccinated subcutaneously with 4 mg. (moist weight) of the virulent vole strain D-15 seven weeks before infection and with 1 mg. of D-15 three weeks before infection. Group II (41 animals) were treated exactly like those of group I except that heat-killed vole bacilli were used. The vole bacilli were heated to 65°C. for thirty minutes. Group III (41 animals) received BCG as the immunizing agent and were given 10 mg. (moist weight) seven weeks before infection and this dose was repeated three weeks before infection. Group IV (32 animals) constituted the control group. As the infecting dose, each animal received subcutaneously 0.000,001 mg. virulent human tubercle bacilli or approximately 1,000 organisms of which 100 were assumed to be viable. This small dose used as immunity in

tuberculosis may be overridden with heavy inocula of virulent bacilli. In groups I and II ulceration occurred at the vaccination site with a discharge of heavy creamy pus. Some of these ulcerations were healed at the end of seven weeks. The BCG animals (group III) showed ulceration and discharge of pus similar to those receiving viable bacilli, but with a more rapid tendency to heal. Fourteen months after infection the experiment was terminated. The results of the infection were as follows: (1) All controls alive after four months developed generalized tuberculosis. At nine months 78 per cent, and at fourteen months 88 per cent had died with generalized tuberculosis. (2) Of the heat-killed vole vaccinated animals, at nine months 35 per cent had died with generalized tuberculosis, at fourteen months 40 per cent. However, 48 per cent showed no gross tuberculosis at necropsy. (3) Of the virulent vole and BCG animals, for the same periods the numbers were roughly 10 per cent and 18 per cent. It is to be noted that at fourteen months 71 per cent of all the viable vole and 50 per cent of all BCG animals were free of gross tuberculosis at the time of death. From the study of microscopic sections it was not possible to say that any difference in protective power existed between the BCG and the viable vole vaccines. There was no significant difference in sensitivity to intracutaneous OT between the vaccinated groups during the period before infection. After infection, in general the greatest tuberculin sensitivity accompanied the greatest degree of infection. The control animals developed the highest degree of sensitivity. No significant differences in tuberculin sensitivity existed between the viable vole and the BCG groups at any stage of the experiment. The heat-killed vole vaccinated animals were somewhat less sensitive than the controls but more sensitive than the others. *Conclusions:* (1) Vaccination with living vole acid-fast bacilli significantly delayed the onset and diminished the severity of experimental tuberculosis in guinea pigs. (2) In the experiment the viable vole bacillus was as

effective as BCG against infection with virulent human tubercle bacilli. There is evidence to suggest that it may be superior to BCG. (3) A heat-killed vole bacillus vaccine showed a less, but still significant, degree of immunizing power. (With 3 plates).—*Immunization with the Vole Acid-Fast Bacillus against Experimental Tuberculosis*, W. S. Brooke & R. Day, *Bull. Johns Hopkins Hosp.*, May, 1944, 74: 275.—(J. S. Woolley)

**Saprophytic Acid-fast Bacilli and Paraffin Oil in Immunization.**—A lanolin-like substance and paraffin oil when combined with horse serum enhanced the formation of antibodies but had little if any effect on sensitization to horse serum. When killed timothy or tubercle bacilli were added to this mixture, both antibody formation and sensitization occurred. Killed timothy bacilli sensitized to tuberculin.—*Saprophytic Acid-fast Bacilli and Paraffin Oil as Adjuvants in Immunization*, J. Freund & Annabel W. Walter, *Proc. Soc. Exper. Biol. & Med.*, May, 1944, 56: 47.—(F. B. Seibert)

**Tuberculo-bacillary Allergy.**—The authors assume, from previous experiments, that "tuberculosis has been resolved into the specific disease, which is closely involved with a developed specific immunity, and a phenomenon also produced by tubercle bacilli in the body, which is the existence of a specific tuberculo-bacillary allergy elicited and produced by the bacillary bodies." In experimental animals the tuberculous bacillary allergy has been differentiated from tuberculin hypersensitiveness. Tuberculin desensitization abolished the local effect of tuberculin but it did not abolish the "accentuated specific allergic-bacillary hypersensitiveness." An attempt was made to accomplish this by the injection of bacillary bodies into "tuberculo-bacillary-allergic hypersensitive" guinea pigs. Repeated intravenous injections of viable avirulent human tubercle bacilli resulted in no appreciable reduction of hypersensitiveness to tuberculin or to viable bacillary bodies but rather in an accentuation of the allergic hyper-

sensitiveness. Likewise, repeated subcutaneous injections of heat-killed tubercle bacilli in mineral oil resulted in only a slight accentuation of the allergic hypersensitiveness. Dead (heat-killed) tubercle bacilli suspended in saline and subcutaneously injected repeatedly showed no appreciable effect upon the tuberculo-bacillary allergic hypersensitiveness. However, when injected intravenously, a depression of the cutaneous allergic hypersensitiveness to tuberculin and bacillary bodies occurred. This could not be attributed to a desensitizing effect but rather was believed to be caused by the effects of the intravenous injection of the bacilli on the general vascular or inflammatory response of the animals. Dead avirulent human tubercle bacilli repeatedly injected intravenously into guinea pigs revealed no appreciable effect on the development of the tuberculous disease resulting from subcutaneous infection with highly virulent human tubercle bacilli; but these same injections appeared to exert a slight detrimental effect on the specific immunity, resulting from vaccination with viable avirulent human tubercle bacilli, which may be accounted for by the ability of the dead bacillary bodies to produce tubercles. "Hypersensitivity" was achieved in the test guinea pigs by injecting a large dose of avirulent human tubercle bacilli one month before the small infecting dose of virulent human bacilli. [In this article clarity has been sacrificed for brevity].—*An Attempt to Desensitize against Tuberculo-Bacillary Allergy*, H. J. Corper & M. L. Cohn, *Am. J. Clin. Path.*, June, 1944, 14: 344.—(J. S. Woolley)

**Allergy.**—The reaction to an intracutaneous injection of an allergenic substance is accompanied by an increase of the local insensible transpiration. This increase is proportionate to the extent of the reacting skin surface. Carefully measured and weighted containers were applied over the site of injection of allergenic substances and the amount of perspiration accumulated was compared to that obtained with an identical procedure over the homologous controlateral part where no injection

tion was given. Over the site of injection the amount of perspiration was considerably increased. This method enables one to express in figures the state of reactivity of the individual.—*Determinazioni allergometriche col metodo della traspirazione latente, C. Bazzicalupo & A. Iaccarino, Riv. di tisiol., 1942, 15: 201.*—(G. Simmons)

**Petragnani's Anatuberculin.**—Patch tests and intracutaneous tests with Petragnani's anatuberculin were made in 138 patients with various forms of tuberculosis and in other diseases. The intracutaneous test was positive in 81 cases, 52 of which had shown a positive patch test also. The cases were thus subdivided: 22 cases of pleurisy with effusion, of which 4 showed complete anergy; 34 cases of active tuberculosis, mainly productive forms; in 8 the patch test was negative, whereas the intracutaneous test was positive; 21 cases of rheumatic fever, only 4 had negative tests; 6 influenza cases, 5 negative; 10 malignant neoplasms, 9 negative; 15 typhoid fever, 4 negative. The remaining 30 cases had various diseases, except tuberculosis, and 45 per cent of them showed an allergic response to anatuberculin.—*L'allergia tubercolare studiata merce l'intradermo e la cutireazione con anatubercolina Petragnani in diversi stati morbosi, M. Pellegrini & N. Carinci, Riv. di pat. e clin. d. tuberc., 1939, 13: 487.*—(G. Simmons)

**Vaccination with Anatuberculin.**—One hundred and seventeen children, most of whom had a positive Mantoux test, were vaccinated with Petragnani's anatuberculin (human tubercle bacilli recently killed, treated with formaldehyde, 1 per cent, neutralized with ammonium hydroxide). This substance is said to be less toxic than ordinary tuberculin and to be able to induce an allergic state of long duration. The children treated were divided into 2 groups: (1) Children with positive anamnestic data and positive Mantoux test. Following the injection of 0.1 cc. of anatuberculin there were slight systemic reactions and a constant local ulceration,

which healed within two or three months. No focal reaction could be seen radiologically. In cases with preëxisting activity of the lesions some improvement was noted. (2) Children with a negative Mantoux test. The initial dose of anatuberculin was 0.1 cc. and this was followed by 0.25 cc. after fifteen days. Moderate systemic reactions, intense local but no focal reactions were observed. Following the second injection a strong allergy, as evidenced by a strongly positive Mantoux test, was established. On the basis of these observations the author concludes that the anatuberculin prepared by Petragnani is a safe substance to be used for diagnostic as well as therapeutic purposes and considers it to be superior to other tuberculins.—*La vaccinazione con l'anatubercolina integrake di Petragnani del bambino allergico con particolare riguardo alla reazione di focolaio, G. Colale, Riv. di pat. e clin. d. tuberc., 1940, 14: 442.*—(G. Simmons)

**New Tuberculin Test.**—For routine testing of school children, the percutaneous method is most desirable. Although Moro's method gives fairly good results, the method has been improved upon by Mérieux of Lyon. He uses cultures of two bovine and two human strains of tubercle bacilli, adds formalin in the proportion 3:1, and reduces the mixture to one-sixtieth of its former volume at a temperature of 37°C. The resultant syrupy fluid is very stable and may be kept for years. A drop of 2 mm. in diameter is applied to a suitably cleansed skin area. Comparing this method with Moro's ointment, 7.4 per cent more positive cases were discovered among a series of 1,100 children tested. The method has not as yet been compared in efficacy to the Mantoux test.—*Das Neo-Tuberkulin Mérieux und seine Anwendung bei Reihen-Untersuchungen, E. Braun, Schweiz. med. Wchnschr., April 8, 1944, 74: 364.*—(H. Marcus)

**Transcutaneous and Intracutaneous Tuberculin Tests.**—A comparison of the transcutaneous and intracutaneous tests was made on 103 patients: 64 tuberculous and 39 non-

tuberculous. To eliminate marked variation in the response to different commercial tuberculins, the autolytic tuberculin and a purified protein tuberculin were prepared from the same original cultures. Among the 103 patients tested, 90 (87 per cent) were positive by the transcutaneous test, and 89 (86 per cent) by the intracutaneous injection. Agreement between the two tests occurred in 82 of the positive tests. When considering the 64 definitely tuberculous cases tested, the agreement was 58 (90 per cent) for the transcutaneous and 62 (96 per cent) for the intracutaneous tests. The slight differences were attributable to the transcutaneous absorption retardation in the definitely ill cases. Among the 39 nontuberculous cases (including those with possible infection but no evident tuberculous disease), the agreement again was fairly close; 32 (82 per cent) reacted to the transcutaneous test as compared with 27 (70 per cent) for the intracutaneous test. There were 7 cases which gave a positive transcutaneous test and a negative intracutaneous test (all grades reaction to 0.001 mg.) and 2 of the latter were positive to the 0.005 mg. test. There were 7 cases which gave a positive (all grades) intracutaneous test and a negative transcutaneous test. The foregoing disagreement in findings brings out several important points with regard to tuberculin tests. Even though highly specific, (1) these tuberculin tests are conditioned by a number of important factors not always controllable no matter which type of test is used; and (2) the importance of repeating a test easily if necessity demands. For this purpose, the transcutaneous test possesses many advantages over any injection test. However, it must be admitted that an intracutaneous test is warranted as a verification test at times, but the transcutaneous test appears to be preferable as a routine either for diagnosis or surveys. The tuberculin test ranks among the best biological diagnostic tests, not as an exclusive test but rather as an inclusive one in addition to other verifying medical findings. It is valuable in specific surveys and as a diagnostic aid in tuberculosis and for the

presence of the hypersensitivity of tuberculous allergy.—*Comparative Results with Transdermal (or Transcutaneous) and Intracutaneous Tuberculin Tests*, H. J. Corper, J. Lab. & Clin. Med., April, 1944, 29: 398.—(F. G. Petrik)

**Patch Test.**—The author analyzed the results of the Vollmer patch test in 487 children aged from two to sixteen years. These children represented 88 per cent of all children born to permanent residents in the town of St. Andrews. There were 340 (69 per cent) negative and 151 (31 per cent) positive results in 491 examinations. Four children were reexamined either because of tuberculosis developing in the family or because of symptoms suggestive of tuberculosis. All 4 had been negative on first examination—3 of them became positive. A breakdown into age groups revealed that 21 per cent of the 0 to five years group, 32 per cent of the six to ten years group and 45 per cent of the over ten years group were positive. An X-ray examination of the chest was made in 131 of the reactors. Five (3.8 per cent) revealed tuberculous lesions of the lungs or pleura, 14 (10.7 per cent) required further observation, 1 (0.8 per cent) revealed a calcified primary focus, 8 (6.1 per cent) showed enlarged hilar nodes, 41 (31.3 per cent) had calcified nodes and in 62 (47.3 per cent) the radiogram was within normal limits. Sixteen negative reactors were also X-rayed. One showed calcified nodes, 2 had enlarged hilar nodes, and the remaining 13 were within normal limits. An analysis as to housing conditions and incidence of reactors failed to reveal any significant differences. One of the children examined was proved bacteriologically to have a bovine infection of lung and kidney, and she was a negative reactor.—*Patch Testing in an East Coast Town*, E. J. Simpson, Brit. M. J., February 26, 1944, 1: 286.—(D. H. Cohen)

**Prevention of Tuberculosis by Ultraviolet Irradiation.**—There is much evidence that human pulmonary tuberculosis is acquired by

the inhalation of minute particles or droplets carrying tubercle bacilli. In a closed space (room) the microorganisms are uniformly distributed throughout the air as proximity to tuberculous guinea pigs shedding tubercle bacilli is not essential for the infection of roommates. Since exposure to ultraviolet radiation kills pure cultures of tubercle bacilli suspended in the air, an attempt was made to determine whether natural airborne contagion of tuberculosis can be prevented by these means. The test animals were from certain inbred rabbit families, frequently described by the author, among which the A family is genetically and uniformly highly resistant to tuberculosis and the C and F families genetically and uniformly show low resistance to the infection. In the study here reported, these three families were used, first, to equalize the natural resistance of the experimental and control animals and, second, to determine whether ultraviolet radiation will have a greater protective influence on the animals of high resistance as compared with those of low resistance. Normal rabbits from the three families mentioned (A, high resistant and C and F, low resistant) were exposed to air-borne contagion from a steady group of rabbits artificially infected with virulent tubercle bacilli and whose cages were only separated from the noninfected rabbits by a space of 6 inches. An air-tight metal partition divided this space (and later the room) transversely at the centre so that one-half of it could be irradiated (ultraviolet lamps), the other part serving as the control or nonirradiated part. To equalize the intensity of irradiation (some cages were nearer the lamps than others) of the air breathed by the contacts, the cages housing them were constantly rotated in an orderly succession. The contacts in the unirradiated half of the cage were also rotated in a similar manner. With some variations, this was the general set-up. The bacilli voided by the infected rabbits are the chief source of the contagion, depending on the bedding used. The results from these experiments were clear-cut and demonstrate the protective influence of ultraviolet irradiation

of the air against natural air-borne contagion of tuberculosis in rabbits. Even when the radiant energy was low it reduced considerably the incidence of tuberculosis, for it completely protected rabbits of high natural resistance from acquiring demonstrable disease, although some of them became tuberculin sensitive. It failed to protect a small proportion of rabbits of low natural resistance from fatal tuberculosis. When the radiant energy was of high intensity, all rabbits, whether of high or of low natural resistance, were almost completely protected from a contagion so severe that it was fatal to the great majority of rabbits of the same genetic constitution not protected by these rays. The contagion of tuberculosis in these studies is air-borne and the radiant energy exercises its protective influence by its bactericidal properties. It is probable that ultraviolet irradiation would control air-borne contagion of human tuberculosis.—*Experimental Epidemiology of Tuberculosis: The Prevention of Natural Air-Borne Contagion of Tuberculosis in Rabbits by Ultraviolet Irradiation*, M. B. Lurie, J. Exper. Med., June, 1944, 77: 559.—(J. S. Woolley)

**Experimental Epidemiology of Tuberculosis.**—In a study of certain inbred rabbit families it became increasingly clear that, if these rabbits were exposed to natural contagion, there was frequently a marked discrepancy between the rapidity with which they acquired tuberculosis on the one hand and the duration of the ensuing disease on the other. The present report deals with these two phases of resistance in the family A, of high inherited resistance to tuberculosis, and the families C and F, of low inherited resistance to the disease. The effect of various concentrations of the contagious agent on these families is also considered. The data analyzed in the paper have been obtained in the course of the past ten years of study of the inherited natural resistance to tuberculosis in these families of rabbits. All were normal rabbits that were exposed to natural air-borne contagion of tuberculosis by living on one side of cages separated in the middle by a wire mesh screen.



On the other side of this screen were placed a certain number of rabbits artificially infected with virulent tubercle bacilli, usually by the intravenous route. Four or 8 infected rabbits served as sources of contagion for 5 or 10 contacts, respectively, depending on the size of the cage which varied in different experiments. The population of the artificially infected rabbits was maintained constant throughout the period of exposure by replacing the dying animals by similarly inoculated rabbits. The urine of these rabbits was examined for tubercle bacilli by direct smear or culture at different periods during the course of their disease. Every two to four weeks the contacts were tested with tuberculin. The onset of the disease in the contacts was dated from the time when the tuberculin reaction became definitely positive. Careful autopsy was performed at time of death. In one experiment, 8 rabbits of high resistance and 7 of low resistance were exposed as indicated and the preallergic and allergic periods, and the type of disease occurring, were noted. While it took an average of 2 months (0.9-3.6) for the members of the resistant A family to become tuberculin sensitive, this preallergic period averaged 4.7 months (1.3-8.3) for the low resistance rabbits. On the other hand, the duration of fatal tuberculosis in the A rabbits averaged 6.4 months (4.1-10.4) while the duration of the disease in the C and F rabbits averaged only 3.5 months (2.1-3.9). Thus, the rabbits of high resistance showed evidence of being infected quickly but died of a chronic, slowly progressive disease, while the members of the families of low resistance showed evidence of being infected slowly but died of a rapidly progressive disease. If we take the onset of allergy as evidence of the beginning of the disease, it is clear that the highly resistant animals are attacked by tuberculosis more quickly than the rabbits of low resistance, but they resist the progress of the ensuing disease more effectively than the latter. It may be questioned, however, whether the development of hypersensitivity to tuberculin is an accurate index of the time of the onset of the disease for occasional animals became allergic, but did not develop dis-

coverable disease. Just how soon tuberculosis began in relation to this onset is, of course, a moot question; but there could not have been much of a delay for the character of the disease in each group, slowly progressive in the resistant and fulminating in the susceptible, fitted in well with the time allotted in the experiment. The author believes that the tuberculin test is a reliable indicator of the duration of the disease, which is all a question of what constitutes disease. In another series of experiments, members of these inbred families of rabbits were exposed to air-borne contagion of varying intensities as measured by the percentage of rabbits used as sources of contagion, which showed tubercle bacilli in the direct smear of the urine at death. One group of 7 resistant and a group of 11 low resistant were exposed to low intensity contagion. None of the former group acquired demonstrable lesions (4 became allergic) after an average exposure of fourteen months. Two of the latter group, with an exposure of six and eleven months respectively, developed rapidly progressive disseminating tuberculosis. Three others became allergic but showed no demonstrable disease. Another group of these families exposed to more severe contagion showed the following: In 6 highly resistant rabbits, 3 acquired a slowly progressive tuberculosis which was fatal in from ten to thirteen months. Five of the 6 became allergic. Of the 11 contacts of low resistance, 10 acquired tuberculosis and accompanying this increase in incidence there was also acceleration of attack (decrease in average preallergic period). In all instances the type of disease was rapidly progressive but did not differ materially from that of the disease in this group in the previous experiment. The final experiment concerns the exposure of these two groups of rabbits to contagion of high intensity. All 7 resistant animals became allergic and 5 of these developed manifest disease. All (5) susceptible animals developed rapidly progressive, disseminating disease. Among the resistant rabbits not only was the incidence of the disease increased but the rapidity of attack was further accelerated and the type of disease acquired fre-

quently partook of some of the qualities characteristic of the families of low resistance. The duration of the disease was also considerably reduced. By contrast the low resistance rabbits differed in no essential respect to this high concentration of tubercle bacilli as compared to their response to the medium concentration. *Conclusions:* (1) Hereditary resistance to attack by air-borne tubercle bacilli is distinct from the resistance to the ensuing disease. (2) One inbred rabbit family has little resistance to attack by the micro-organism but has considerable resistance against the ensuing disease. (3) Another inbred family has considerable resistance against attack by the tubercle bacillus but has little resistance against the ensuing disease. (4) Increasing concentrations of tubercle bacilli in the environment of the family of high genetic resistance to the disease increase the incidence of infection, accelerate the onset of the disease, and affect its essential character in proportion to the concentration of the microorganism. (5) Up to a certain concentration of tubercle bacilli in the environment of the families of low genetic resistance to the disease, increasing concentrations of the infectious agent also increase the incidence of the disease and accelerate its onset, although its anatomical character is always of a uniform rapidly progressive type. Beyond this concentration further increment of the infectious agent exercises no effect.—*Experimental Epidemiology of Tuberculosis: Hereditary Resistance to Attack by Tuberculosis and to the Ensuing Disease and the Effect of the Concentration of Tubercle Bacilli upon these Two Phases of Resistance*, M. B. Lurie, J. Exper. Med., June, 1944, 79: 573.—(J. S. Woolley)

**Chemotherapy in Experimental Tuberculosis.**—Among the chemical agents found most effective in combating tuberculosis in experimental guinea pigs, derivatives of 4,4'-diaminodiphenylsulphone are best. The drug has little taste and can be mixed with the feed without impairing its palatability. It is absorbed slowly from the gastro-intestinal tract and persists longer in the blood stream than most sulphamides. A study was under-

taken to determine its effect in experimental tuberculosis. Three experiments were run. In two the drug was started two days before inoculation of the guinea pigs with tubercle bacilli, and the experiments terminated sixty days later. In the third experiment, animals were inoculated with tubercle bacilli, and treatment was started six weeks later. In all animals the virulent variant of H37, H37RV, was used. The daily dose of the drug was 150 mg. mixed with the feed. In the first two experiments 3 treated animals died, and the cause of death was not apparent but was assumed to be due to the toxic effect of the drug. When the third experiment was terminated 228 days after inoculation, 71.4 per cent of the untreated animals had died from sufficient tuberculosis to cause death, and 71.4 per cent of treated animals were living. Of the 4 dying in the latter group, one died from tuberculosis while in the other 3 the cause of death was not apparent, though each animal had minimal disease only. The relative amounts of tuberculosis present in treated and untreated groups, evaluated numerically, showed a marked difference in the character and amount of the disease. In the first two experiments, the average index of infection among the treated animals was 12.1 and 14.1 as compared to 76.4 and 71.4 in the two untreated groups. If the site of inoculation is disregarded, the indexes would be 66.4 for the untreated and 7.9 for the treated in group II. In the long-term experiment the difference is even more striking, the index of infection averaging 84.1 in the untreated animals and 8.4 in the treated. Of importance also is the fact that in 6 of the 13 treated guinea pigs tuberculous lesions were absent in liver, spleen and lungs, grossly and microscopically, as compared to one in 28 in the untreated group. The pathological changes are even more interesting. In the first two experiments the aggressive character of the disease in the untreated controls was in sharp contrast to the focal and relatively few and small lesion in the treated group. Necrosis, when present, was minimal in amount. The changes that occurred in both groups of experiment three was even more dramatic.

The character of disease in the untreated animals was that of an apparently uninhibited process occupying most, if not all of the organs of predilection. Necrobiosis was a constant and striking feature so that, in some, the histological landmarks were obliterated. Among the treated animals in this group, there were a relatively few nonprogressive residual lesions found in the organs of predilection. A tendency of the axillary lymph node lesions to calcify was noted, and only a few nodules and hard tubercles were found in the spleen and lung. Sensitivity to tuberculin was greater in the untreated than in the treated, and among the latter group those with indefinite or negative tests showed nonprogressive or no demonstrable lesions. Attempts were made to culture tubercle bacilli from the spleens. In experiments one and two, 12 cultures were positive out of 14 in the untreated group and one in 13 of the treated group of experiment one, while in the second group, 9 in 10 of the untreated and 2 in 7 of the treated were positive. Thus, from 24 untreated animals 21 cultures were positive, while from the 20 treated ones, 3 were positive. No attempt was made to obtain detailed information regarding the blood, but cardiac blood was obtained at the termination of the experiment in 8 animals of the control group, and 6 of those treated for one hundred and eighty-six days. Examinations revealed that definite destruction of erythrocytes was caused by the drug, but there was a marked degree of macrocytosis indicating rapid regeneration. There was also a high per cent (10.3 per cent) of reticulocytes in the treated group.—*The Effects on Experimental Tuberculosis of 4,4'-diaminodiphenylsulphone*, W. H. Feldman, H. C. Hinshaw & H. E. Moses, *Am. J. M. Sc.*, March, 1944, 207: 290.—(G. F. Mitchell)

**Diet and Toxicity of Promin.**—Promin has been shown to be an effective chemotherapeutic agent in the control of experimental tuberculosis. Since the drug does induce certain toxic reactions in the experimental animal, any measures which may reduce the extent of these reactions without minimizing the therapeutic value of the drug, may prove

to be of clinical importance. Self-selection experiments have shown that young rats given promin daily appeared to crave some of the fractions of vitamin B. Also, recent studies have shown that foods high in their vitamin B content may modify or even nullify the toxic influences of some of the sulfone drugs. A study of feeding purified diets, and purified diets fortified by whole liver or brewers' yeast, to white rats receiving 50 mg. of promin daily is reported. The following conclusions are reached: Animals which ate the purified high protein diet gained more weight during the time promin was given than those which ate the purified high carbohydrate diet. Animals which ate the high carbohydrate diet supplemented by whole liver gained nearly four times as much as those eating the high carbohydrate diet alone, during the time promin was given. Animals which ate the purified high protein diet supplemented by brewers' yeast gained twice as much as those eating the high protein diet alone, during the time promin was given. The administration of liver extract (Campolon) was accompanied by a marked decrease of weight during the first week of administration of promin. Liver extract was far less effective than whole liver. Loss of hair and hyperirritability occurred in both groups eating either the purified high protein or the high carbohydrate diet. These symptoms did not occur when the drug was given to animals eating the diet plus whole liver. Rather extensive alopecia developed in animals given the liver extract. The concentration of promin in the blood of all animals examined the day following the last administration of promin was highest in those which received the liver extract. It was lowest in those which ate the diet containing the whole liver supplement. The most marked anemia occurred in animals which ate the purified high carbohydrate diet. Slightly better values were obtained in rats which ate the high protein diet. The supplementation of the diets by either whole liver or yeast greatly improved the blood picture.—*The Influence of Purified Diets upon the Toxicity of Promin*, G. M. Higgins, *Am. J. Clin. Path.*, May, 1944, 14: 278.—(J. S. Woolley)

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**Tuberculous Bacilluria.**—The urine of 30 patients with advanced cavernous tuberculosis of the lungs was examined for tubercle bacilli for a period of over three years. Twenty patients died and came to autopsy. In 5 cases with positive urine findings during life, tuberculous lesions of the urinary tract were found. In 4 cases tuberculous lesions were found in spite of persistently negative urinary findings during life. In 10 cases the examinations during life and the pathological findings were negative. In 5 cases with positive findings during life, no tuberculous lesions were found at autopsy. Histological examinations were based on careful studies of serial micro-sections of the renal papillae and of the pyramids. In connection with this examination bacillemia was induced experimentally in rabbits by intravenous injection of suspensions of tubercle bacilli. The twenty-four-hour urine of the animals was collected and cultures of an egg-asparagin smear were inoculated into guinea pigs. While tubercle bacilli were present in the blood of a series of these infected animals, bacilli could not be recovered from the urine. Histologically the kidneys proved to be negative. The authors conclude that tubercle bacilli may pass through the kidneys of patients with pulmonary tuberculosis at the terminal stage of the disease even in the absence of local renal lesions.—*Bacilluria tuberculosa*, M. F. Magarao, P. F. de Albuquerque & C. de Paz, Jr., *Rev. méd. munic.*, March, 1943, 5: 253.—(F. G. Kautz)

**Tubercle Bacilluria.**—The problem of the filtrability of tubercle bacilli through the

normal kidney is an old one and experimental results are controversial. The author induced diuresis in rabbits and, following the intravenous injection of tubercle bacilli, was able to demonstrate, by subsequent injection of guinea pigs, that 33 per cent of the rabbits' urines collected twenty to thirty minutes after the injection of bacilli contained tubercle bacilli. Filtrability of tubercle bacilli through the normal kidney of a rabbit is therefore possible, provided, however, that the bacillemia is of a certain degree and the kidneys are in a state of hyperfunction and provided also that the bacilli are looked for shortly after the onset of the bacillemia. If confirmed for men, these findings may be significant, in as far as they may indicate that tubercle bacilli may be found in the urine, although no specific involvement of the kidneys exists.—*Dimostrazione della filtrabilità del bacillo di Koch attraverso il rene sano durante poliuria sperimentale*, A. Rubino, *Riv. di tisiol.*, 1940, 13: 459.—(G. Simmons)

**Tubercle Bacilluria.**—Tubercle bacilli cannot pass the intact kidney. Systematic examinations show that minute foci of caseation can be found in the kidneys of patients dying of tuberculosis of the lungs who never manifested tuberculosis of the genito-urinary tract. These lesions are usually located in the glomeruli. Small scars are also frequently encountered at autopsy of tuberculous patients, adding weight to the contention that renal lesions are rather frequent but usually heal. Children with tubercle bacilluria always have positive tuberculin reactions. They

frequently have cervical lymph node enlargement indicating that the lymphatic barrier has been passed. Renal tuberculosis is due to both bovine and human tubercle bacilli. Although most renal lesions undoubtedly heal without specific treatment, sanatorium treatment, tuberculin ointment and vitamin C are advised for children. A common symptom of renal tuberculosis in children is enuresis. This disappears with the improvement in the kidney condition and as the general condition improves the bacilluria disappears.—*Tubercle Bacilluria, Annotation, Lancet, July 1, 1944, 257: 22.*—(H. Marcus)

**Mode of Tuberculous Infection.**—Ninety per cent of tuberculosis is contracted by means of inhalation. Droplet infection does not play a large rôle in this connection. Inhalation of dust containing dried tubercle bacilli seems to cause the majority of cases. The larger droplets, if inhaled, seem to cause those rare cases of tuberculosis of the pharynx and tonsils. Droplets rarely reach the lung. Bovine tubercle bacilli are fully as virulent for humans as the human strain, but usually cause disease in extrapulmonary locations. In countries where the destruction of tuberculous cattle is not obligatory, a higher percentage of cases is caused by bovine bacilli, and the source of tuberculosis is, therefore, found in the gastrointestinal tract.—*Wie bekommt der Mensch eine Infektion mit Tuberkelbazillen?, A. Gigon, Schweiz. med. Wchnschr., May 13, 1944, 74: 532.*—(H. Marcus)

**Blood Calcium in Tuberculosis.**—The values of the concentration of serum calcium in normal Bengali male adults were found to vary very little. The average calcium content in the serum in early and advanced pulmonary tuberculosis fails to show any significant variation from that of the normal blood. In some advanced cases with high temperatures the calcium level was decreased. This probably was due to increased adrenalin released during the fever or to extreme loss in the stools in the presence of diarrhea. In various types of tuberculosis of the bones and joints with

destructive or atrophic lesions there was neither hypercalcemia nor hypocalcemia.—*A Study of Blood Calcium in Tuberculosis, S. K. Sircar & B. Lahiri, Indian M. J., August, 1943, 37: 114.*—(F. G. Kautz)

**Plasma Lipase in Tuberculosis.**—In at least 5 papers the problem of the relationship between the plasma lipase and course of pulmonary tuberculosis is being studied. So far the importance of the lipase was considered because it was thought that this enzyme may be able to destroy the fat capsule of tubercle bacilli. There is, however, no relation between the form and gravity of the disease and the absolute value of the plasma lipase. The lipase circulating in the blood is not one definite substance, but a mixture of different lipases, elaborated in and eliminated by different organs. A study of the lipase content of the plasma, therefore, may give information as to the metabolic activity of certain organs, if studied repeatedly over a prolonged period of time. The metabolic activity, on the other hand, may be considered indicative of the resistance of the diseased organism toward tuberculosis. The common laboratory methods for the determination of lipase being unsuitable for large scale studies, the author developed a special technique, which is less time consuming. More than 30 determinations can be done with his method during one morning and the amount of blood required for each test is 2 cc. Studying the plasma lipase in about 80 patients with pulmonary tuberculosis over several months, repeating the test once a month, it was found that there is a definite relationship between the course of the disease and the progressive changes in the lipase content of the blood. An increase of the lipase goes parallel with an increasing bodily resistance and an improvement of the pulmonary condition, whereas a progressive decrease is indicative of failing resistance and of poor prognosis. The lipase being in relation with the intensity and orientation of the general metabolism and the sedimentation rate corresponding to the degree of intoxication of the organism, both the lipase and the

sedimentation rate are determined in order to better evaluate the progress of the disease. The following combinations are possible: (1) High lipase content with normal sedimentation rate. This is the group of patients with high resistance and inactivity of the pulmonary process. (2) Low lipase and high sedimentation rate, the resistance is low and the lesions are very active. (3) High lipase and high sedimentation rate, both resistance and activity of the disease are great. (4) Low lipase and low sedimentation rate. This is the group of patients in whom, despite satisfactory collapse, the general condition does not improve once it is poor. Whereas one single determination of the lipase has no importance, the study of changes in the concentration of this enzyme in the blood, together with a study of the changes in the sedimentation rate, has proved to be of great prognostic importance and is being routinely used in one of the largest sanatoria in Italy. According to Scholz lipase is able to hydrolyze the fat capsule of the tubercle bacillus and the variations in the lipase content of the blood are parallel to those in the lipase content of the diseased organs. The same author believes that ascorbic acid is the agon of the esterases and that intake of ascorbic acid causes an increase in the lipase content of the plasma. Scoz has repeated the experiments and arrived at the conclusion that ascorbic acid has no direct relation to the lipase of the blood.—*Le lipasi del plasma nei malati di tubercolosi polmonare, Nota 1: Introduzione; Nota 2: Metodo di determinazione titrimetrica; Nota 3: La lipasi del plasma nei malati di tubercolosi polmonare; Nota 4: Influenza dell'acido ascorbico, G. Scoz, Riv. di tisiol., 1941, 14: 221 and 253.*—(G. Simmons)

**Nicotinic Acid in Tuberculosis.**—Nicotinic acid has proved valuable in the treatment of severe diarrhea of patients with pulmonary tuberculosis. Diarrhea and other gastroenteric disturbances of long standing disappeared rapidly in 16 out of 30 patients. It is assumed that nicotinic acid is useful whenever diarrhea is not caused by specific intestinal

disease but is due to toxemia, eventually resulting in avitaminosis.—*L'acido nicotinico nella cura della diarrea degli ammalati di tubercolosi polmonare, G. Chiti, Riv. di tisiol., 1941, 14: 415.*—(G. Simmons)

**Vitamin K during Hemoptysis.**—The coagulation time is prolonged in 90 per cent of patients with pulmonary hemorrhage; the prolongation in 28 per cent of them was so considerable (up to 100 per cent) that it was probably an important cause for the hemoptysis. The intake of synthetic vitamin K causes almost invariably the return to normal of the coagulation time, but this effect persists only as long as the vitamin is being taken. Although "the treatment (with vitamin K) is frequently followed by the disappearance or the attenuation of the hemoptysis," in some cases the hemorrhage starts in patients in whom the coagulation time is normal or had been made normal previously.—*Sui primi 36 casi di emottisi tubercolare trattati con vitamina K, G. Scoz & L. Castaldi, Riv. di tisiol., 1940, 13: 314.*—(G. Simmons)

**Vitamin K in Tuberculosis.**—Prolongation of the prothrombin time is seen only in a relatively small percentage of sanatorium patients with tuberculosis. The cases that do show prolongation are generally those with active disease, often with gastrointestinal involvement. Out of 58 cases, 16 per cent showed a prolongation. Patients with massive hemorrhage do not, as a rule, show abnormal prolongation of prothrombin time, but among 6 patients with minor pulmonary bleeding 3 had abnormally long prothrombin times. Drop in the blood prothrombin content is seen regularly after operation on tuberculous patients, and this drop cannot be influenced by the administration of vitamin K pre- or postoperatively. In general, prothrombin values in tuberculosis are approximately the same as in normal people and no definite value of vitamin-K therapy in tuberculosis has been established.—*Untersuchungen über das Vitamin K bei Tuberkulose, E. Tanner & F. Suler, Schweiz. med. Wchnschr., May 20, 1944, 74: 552.*—(H. Marcus)

**Plasma Globulin and Sedimentation Rate.**—Studying changes in the concentration of globulin of the blood plasma and the erythrocyte sedimentation rate over a long period of time in patients with different forms of pulmonary tuberculosis, showed that the globulins do not influence the sedimentation rate.—

*Velocità di sedimentazione del sangue e concentrazione delle globuline del plasma, G. Scoz & A. Guzzi, Riv. di fisiol., 1943, 16: 3.*—(G. Simmons)

**X-rays and Sedimentation Rate.**—The sedimentation rate in patients with pulmonary tuberculosis shows variations according to the patient's physical activity, showing a decrease in those cases in which the evolution of the disease is favorable and showing an increase in cases of progressive tuberculosis. X-rays applied to the region of the spleen cause similar changes of the sedimentation rate. Both a standardized physical exercise and exposure to a definite amount of X-rays were used in a group of 25 patients for prognostic purposes and to determine the amount of work these patients may be permitted to perform. Both tests gave parallel results and it is believed that the X-ray test may be of value for the diagnosis and prognostication of pulmonary tuberculosis.—*Influenza delle irradiazioni roentgen sulla curva sedimentaria, A. Jaccariono, Riv. di fisiol., 1942, 15: 114.*—(G. Simmons)

**Respiratory Centre and Hydrogen Ion Concentration.**—The ability to compensate for a gradually increasing acidosis due to intravenous injections of hydrochloric or lactic acids was tested in anesthetized dogs deprived of their chemoreceptor reflexes by denervation of the carotid sinus region and by section of both vagus nerves. Test of the ineffectiveness of the chemoreceptor reflexes was made by finding that the usual hyperventilation due to breathing oxygen of low tension was replaced after denervation by a depression. Results in all experiments were similar. The existing acidosis, as shown by the lowering of the bicarbonate concentration of arterial blood, was compensated for by increased ventilation and

a consequent lowering of the CO<sub>2</sub> tension of arterial blood, the latter being in inverse proportion to the volume of ventilation. The compensation may be efficient enough to maintain the pH of arterial blood constant at least within  $\pm 0.01$ . As the chemoreceptors in the experimental animals were ineffective, we will have to accept the respiratory centre as the regulatory mechanism, unless we invoke some other unknown mechanism, and therefore the respiratory centre must be sensitive to changes in hydrogen ion concentration at least as small as pH 0.01. A speculative hypothesis is presented. It postulates the existence in the respiratory centre of two mechanisms, one that would originate impulses under the stimulus of increased hydrogen ion concentration, while a second would respond to afferent reflex impulses. These mechanisms might act both independently and additively and might be found either in the same or in separate cells. (Author's Summary.)—*The Sensitivity of the Respiratory Center to Hydrogen Ion Concentration, M. G. Banus, H. H. Corman, V. P. Perlo & G. L. Popkin, Am. J. Physiol., August, 1944, 142: 121.*—(G. C. Leiner)

**Artificial Respiration.**—This study comprises an experimental attempt to determine which methods of artificial respiration are more efficient. The aim of all methods of artificial respiration is the maintenance of respiratory exchanges in the nervous system. For this, two fundamental requirements must be fulfilled: (1) adequate pulmonary ventilation; and (2) transport of respiratory gases from air to the lungs. Thus the fundamental fact to be considered is the assessing of the value of oxygen which can be transported to and used by the tissues. In this study dogs prepared, either by spinal transection between the first and second cervical segments or deeply anesthetized with nembutal so that the medullary centres were inactive, were used. In either method, artificial respiration was maintained by a pump except when manual methods were being investigated. The two methods studied were the traditional

abdominal pressure respiration of Schafer and the newer "rocking method." In the latter, after the dog is firmly strapped to a board, rocking is carried out symmetrically about a horizontal axis through the centre of the board. A rate of 8 to 10 respirations a minute was made with constant velocity. Using these methods, the rates of oxygen-intake, tidal air, ventilation volume, arterial blood pressure and cardiac output were measured. Although tidal air and ventilation by the Schafer method were only about 50 per cent of those with the rocking method, there was little difference in the rate of oxygen-uptake. The authors conclude from this that the ventilation factor is not the important one in assessing the oxygen-uptake, but that the cardiac output is a rather important factor. It is further concluded that the rate of oxygen-uptake and the cardiac output are greater with the rocking method than with the Schafer; the oxygen tension of the venous blood is higher. Despite the apparent greater efficiency of the rocking method over the Schafer method, the authors agree that the latter method should be immediately instituted when resuscitation is undertaken and no time should be lost while preparations are being made for the use of any other method.—*An Experimental Study of Different Methods of Artificial Respiration*, A. Hemingway & E. Neil, *Brit. M. J.*, June 24, 1944, 1: 833.—(D. H. Cohen)

**Hyperpnea of Muscular Exercise.**—Among the earliest explanations proposed for the control of respiration was that of Volkmann in 1841 and Vierordt in 1844, who believed that respiration was regulated chiefly by means of reflexes. One hundred years later this explanation again seems to be satisfactory though resting now on far firmer experimental support. In the intervening years all theories dealing with the control of respiration were concerned chiefly with the dominant effect of chemical substances acting directly upon the medullary centres. Probably the most important discovery of the last century—more important than the finding of any new

reflex or chemical stimulant—has been the realization that respiration is controlled not by reflexes alone, not by chemical stimulation of the medulla alone, but by the proper interaction of both factors. No reflex, no matter how strong, can stimulate respiration if the arterial  $\text{CO}_2$  tension has been lowered abnormally; no chemical stimulant, no matter how great, can produce rhythmic breathing if the medullary centres have been completely cut off from all nervous influences including that residing in the pneumotaxic centre. Respiratory alterations in general, and the hyperpnea of exercise in particular, cannot be explained by any single simple theory but only by a consideration of a number of known and probably many unidentified factors. (Author's Summary).—*The Hyperpnea of Muscular Exercise*, J. H. Comroe, *Physiol. Rev.*, July, 1944, 24: 319.—(G. C. Leiner)

**Lung Expansion.**—Measurement of the vital capacity by means of the spirometer is a valuable test to determine the breathing capacity of recruits. Because of the difficulty in transporting spirometers a simple way of determining lung expansion with the help of a few measurements has been devised. The total increase in the volume of the trunk in inspiration is a fair measure of vital capacity, and it is therefore termed lung expansion. It is assumed that the upper part of the chest is a cone, with its apex at the suprasternal notch, and its base at the level of the nipples. The abdomen from the umbilicus to the symphysis pubis is a similar cone. The parts from the nipples to the xyphoid and from the xyphoid to the umbilicus are truncated cones. Each cone is a quarter of the length of the trunk. The important measurements are circumference of the chest at the nipple line ( $a$ ), circumference of the chest at the xyphoid ( $b$ ), circumference at the umbilicus ( $c$ ), and length of the trunk from the suprasternal notch to the symphysis pubis ( $L$ ). The volume of the trunk then equals  $\frac{L}{48\pi} (2a^2 + 2b^2 + 2c^2 + ab + bc)$ . Tables have been constructed to show the expression



$\frac{L}{48\pi} 2 \times 2$  for all values of adult trunk measurements so that the total volume can be easily calculated from adding these expressions. The mean probable error in the method is 8.7 per cent, and the values closely resemble measurements of vital capacity by means of the spirometer. This method was applied to the testing of recruits before and after training. The recruits were subdivided into four groups for this purpose: the athletic group, the active group, the never active men and the effort intolerant men. It is most convenient to express the findings in terms of volume per square meter of body surface. From the results it appears that any man having 1,900 cc. of lung expansion per square meter of body surface should be capable of the exertion required of a front-line soldier. If the lung expansion is less than 1,100 cc., the soldier is incapable of such efforts. It was found that some men with expansions of less than 1,800 cc. improved their expansion to a value above this in the course of training and passed the required endurance test. Some men with values slightly below this passed the test after training without, however, improving their expansion. The bulk of the men who passed the test had expansions of 1,800 cc. or above. It is concluded that measurement of lung expansion and relating it to the body surface is a valuable adjunct in estimating a man's capacity for infantry training.—*Calculation of Lung Expansion*, H. K. Goadby, *Lancet*, September 23, 1944, 247: 415.—(H. Marcus)

**Pulmonary Permeability in Pulmonary Tuberculosis.**—This paper is based upon an earlier communication by Knipping who developed a method for the determination of functional pulmonary insufficiency caused by a disturbed pulmonary permeability. In a normal individual the margin of safety is sufficiently large, so that exposure to air containing more or less than 21 per cent of oxygen does not produce any change in the absorption of oxygen during rest, as well as during exercise. In patients, however, in

whom the permeability is decreased and who, therefore, are in a state of more or less latent anoxia, exposure to an increased concentration of oxygen leads to an increased absorption of this gas. This latent anoxia, furthermore, may be enhanced and made evident by reducing the oxygen content of the inspired air-mixture. The author believes that changes in the absorption of oxygen thus obtained are a good indication of the damage of the pulmonary permeability and he is inclined to consider it in the evaluation of the clinical-pathological picture, as well as in the estimation of work that the patient may be allowed to perform safely. A simple apparatus is described which enables the author to produce and maintain a certain concentration of oxygen for the duration of this functional test.—*Esame della permeabilità polmonare nei malati di tubercolosi polmonare*, G. Scoz, *Riv. di fisiol.*, 1940, 13: 333.—(G. Simmons)

**Red Cells under Various Oxygen Tensions.**—This is another study designed to produce or make evident a state of respiratory insufficiency in patients with pulmonary tuberculosis in order to obtain an idea of the degree of the disturbed pulmonary permeability and thus to estimate better the degree of activity which the patient may be allowed. The authors found that in normal individuals and in patients in whom there is no latent respiratory insufficiency there is no change in the consumption of oxygen, the pulmonary ventilation or the number of erythrocytes, while breathing mixtures of different concentrations of oxygen. In patients with a latent respiratory insufficiency, however, there occurs first an increase in pulmonary ventilation, when the oxygen content of the inspired air is lowered to 15 per cent. The increase in pulmonary ventilation is apparently designed to increase the oxygen tension in the alveolar air. In addition an increase of the red blood cells occurs which is interpreted as a humoral mechanism of compensation, arrived at to compensate for an incipient state of anoxia. The intensity of these compensatory mechanisms is the more pronounced the severer the

latent respiratory insufficiency is.—*Il numero di globuli rossi nel tubercolotico, che respira in ossigeno al 15, 21 e al 50 per cent, G. Scoz & E. Filla, Riv. di tisiol., 1940, 13: 447.*—(G. Simmons)

**Pulmonary Stasis and Tuberculosis.**—In a number of rabbits ligation of an upper pulmonary lobe was performed before and after the animals were inoculated with tubercle bacilli. The ligation was sufficient to cause stenosis of the involved bronchus and occlusion of the collateral circulation between the bronchial and pulmonary vessels. Although it was not tight enough to cause compression of the pulmonary arteries, it caused compression of the veins and a corresponding increase of the blood-pressure in the pulmonary circulation. This procedure is said to have brought about a noteworthy influence upon the local evolution of the experimental tuberculosis. In the majority of animals the specific lesions were fewer and less extensive than in control animals. In 25 per cent of the rabbits, however, total caseation of the ligated lobe and symphysis of the overlying pleura occurred. In the latter cases microscopic examination revealed a nonspecific reaction with fibrosis all around the necrotic foci, the bronchi and the vessels. Such a reaction was never encountered in the control animals. Whereas there was no difference in the life span in operated animals and in control animals when massive doses of bacilli had been inoculated, the former survived the latter for more than one-third of the duration of the infection when the number of bacilli injected was small. The operative trauma, which had no effect on healthy rabbits, caused a fatal shock in 4 out of 14 animals which had been infected with tuberculosis prior to the operative intervention.—*Influenza della stasi polmonare nella tubercolosi sperimentale, F. Guerriero & V. De Franciscis, Riv. di pat. e clin. d. tuberc., 1940, 14: 357.*—(G. Simmons)

**Venous Pressure in Pulmonary Fibrosis.**—In the majority of cases of unilateral pulmonary fibrosis due to tuberculosis there is a

difference in the venous pressure as determined in both arms. The venous pressure is considerably lower on the side where the fibrosis had occurred. Due to differences in the anatomical position of the veins, the venous pressure is usually lower on the right; the lowest values in a series of 21 patients studied were encountered in a case of a right fibrothorax. In cases with a mediastinal shift this lowering of the venous pressure is less evident; as a matter of fact, an increased pressure may be observed at times.—*La determinazione della pressione venosa bilaterale nelle sindromi retrattive primarie monolaterali di natura tubercolare, C. Panizzoni, Riv. di tisiol., 1942, 15: 213.*—(G. Simmons)

**One-Stage Operation for Putrid Lung Abscess.**—The authors believe that morbidity and mortality in acute putrid abscess are due to the type of operation used and not to the disease itself, and they stress the low mortality and high degree of complete success with the one-stage operation. Except for abscess facing fissures, diaphragm or mediastinum, adhesions are present in seven to ten days and the abscess can be opened in one stage. Precise roentgenography is necessary for accurate localization and, for this purpose, two sets of films are taken—one to localize the abscess, the second after injection of a mixture of iodized oil and methylene blue into the parietes at the point of contact with the abscess. They stress the importance of complete unroofing of the abscess and of all recesses. Inadvertent entry of the free pleural space is treated by converting the small opening into a larger one, broadly suturing the lung surrounding the abscess to the thoracic musculature and placing a gauze pack over the suture line. In abscess without visceroparietal adhesions (abscess facing fissure, etc.) the one-stage operation is also used. A liberal opening in the free pleura is effected, with broad suturing of normal lung to the thoracic parietes. A gauze strip is laid over the suture line and the free pleural space thereby scaled off. The abscess is then needled and opened into. To prove their contention that morbidity and

mortality are due to the type of operation used and not to other factors, they cite the results of 162 cases of acute putrid abscess of their own. There was no selection and many were very severe. The mortality was 2.47 per cent. There were only 4 deaths, 3 of which they ascribe to infection due to errors in technique. In only one case was death ascribable to the disease itself. Complications were few and complete cure obtained in the great majority of cases. Only 3 cases of empyema occurred in the entire series and these comprise errors in operative technique. Where the free pleural space was intentionally entered (over 12 cases), not a single instance of pleural infection resulted. The necessity for secondary operations they also ascribe to errors in technique and not to the disease itself. The follow-up of all their cases over many years has established the fact that permanent cure followed the described operation. They call attention to the fact that the one-stage operation was used successfully in every case of nonputrid abscess also (22), with lasting cure in all of them.—*Acute Putrid Abscess of the Lung*, H. Neuhoj & E. Hurwitz, *Ann. Surg.*, October, 1943, 118: 656.—(D. J. Rednor)

**Resection for Pulmonary Abscess.**—The author presents a series of 66 cases and contrasts the low mortality (4.5 per cent) and excellent end-results of acute abscess with the high mortality (22.8 per cent) and poorer end-results in chronic abscess. In the chronic abscess group, primary lung resection was accompanied by a lower mortality (7.1 per cent) and better end-results than other types of treatment. Secondary resection following previous drainage operations salvaged otherwise unsuccessful cases and resulted in no immediate mortality, but a higher incidence of late complications and deaths increased the eventual mortality of all resections to 12.5 per cent, as compared with 22.8 per cent mortality in the entire group of chronic abscess cases treated surgically. The duration of the chronic cases was three months to several years from the onset of symptoms.

A large percentage of patients therefore presented complications—multiple abscesses, chronic organizing pneumonitis with fibrosis and atelectasis, bronchiectasis, perforation with encapsulated empyema. In such cases, simple pneumonotomy resulted in improvement, but incomplete recovery, and the advisability of secondary pulmonary resection is suggested. From the author's series and the reports of others, he believes primary resection without preliminary drainage to be the procedure of first choice in chronic abscess if one or more of the following conditions exists: (1) multiple abscesses or extensive destruction in one or more lobes, (2) secondary bronchiectasis, (3) atelectasis and pneumonitis unrelieved by bronchoscopic treatment, (4) uncontrolled bleeding, (5) perforation and localized empyema. In respect to the latter complication, the evacuation of the empyema and resection of the involved lobe in a single-stage operation was deemed technically feasible and reasonably safe. The operative technique is described in detail.—*The Surgical Treatment of Chronic Pulmonary Abscess*, G. E. Lindskog, *Surgery*, May, 1944, 15: 783.—(D. J. Rednor)

**Lung Abscess and Influenza.**—The author analyzed 17 cases of influenzal pneumonia occurring during the recent epidemic. The ages varied from twelve to sixty years. There were 5 deaths. In 5 cases lung abscess developed and 3 of these died. A study of the abscess cases revealed *Staph. aureus* to be the main constituent of the sputum. Treatment was with sulphadiazine, sulphamezathine, and sulphapyridine with the usual poor results noted in cases of influenzal pneumonia. Necropsy revealed that in the first case the right lung showed confluent bronchopneumonia with numerous abscesses 0.5 cm. in diameter in the anterior half of the upper lobe, and purulent bronchitis, as well as sero-fibrinous pleurisy. The second case—a twenty year old female munition worker, revealed a mucopurulent bronchitis; the right middle lobe showed gray consolidation, in front of which was a superficial acute abscess

5 x 4 x 4 cm. extending nearly to the midline behind the sternum. There was spread of pus to the mediastinum above the base of the heart, with two small secondary abscesses here, near enlarged lymph nodes. A fibrinous pericarditis and two brain abscesses were also discovered. In the third fatal case necropsy was refused. The 2 patients who recovered had a long recovery period despite intense therapy.—*Lung Abscess in Relation to the Influenza Epidemic*, E. David, *Brit. M. J.*, March 25, 1944, 1: 416.—(D. H. Cohen)

**Radiology of Bronchiectasis.**—In acquired bronchiectasis the flat X-ray film may show no abnormalities at all or the following signs: depression of the interlobar fissure, without distortion; abnormal bronchi, visible as parallel lines or radiotranslucent circles; honeycombing due to dilated bronchi and some surrounding pneumonitis; clouding due to pneumonitic changes. Atelectasis, emphysema, fibrosis, enlarged hilar shadows, pulmonary tuberculosis may be seen. Radiological findings in congenital bronchiectasis are: multiple annular shadows with or without fluid levels; isolated annular shadows; a well rounded opacity due to a cyst filled with fluid; obscuring of an entire lung field. Bronchographic examination permits the differentiation of acquired bronchiectases into cylindrical, saccular and varicose ones. Blunting together with crowding of bronchi is indicative of bronchiectasis. In congenital bronchiectasis, the small cysts always fill with lipiodol; the bigger, isolated cysts fill with much more difficulty.—*The Radiology of Bronchiectasis*, S. F. Oosthuizen, *Clin. Proc.*, Cape Town, March, 1944, 3: 133.—(G. C. Leiner)

**Inhalation of Sulfathiazole.**—Fifty ambulatory or semi-ambulatory white male adults, employees of the Panama Canal or in the military service of the United States, were selected for treatment on the basis of the following criteria: cough and expectoration of more than six weeks' duration, lack of response to previous therapy and presence of

bronchial lesions of bacterial origin. A 5 per cent solution of sodium sulfathiazole was placed in a nebulizer and the rate of flow was maintained at 4 liters per minute by connecting the nebulizer to an oxygen tank equipped with a flow-meter. The patients inhaled the material for twenty-minute periods three times daily over a ten-day period. Approximately 2 cc. were used in a single treatment. Toxic reactions occurred in 2 cases, but consisted only of discomfort and swelling of the nasopharyngeal mucosa. Five case histories are presented. The procedure failed completely in bronchial asthma due to nonbacterial inhalants. Forty-three cases, or 86 per cent of the series, showed definite improvement.—*Treatment of Bronchial Lesions by the Inhalation of Nebulized Solution of Sodium Sulfathiazole*, I. L. Applebaum, *Dis. of Chest.*, September-October, 1944, 10: 415.—(K. R. Boucot)

**Sulfonamides in Bronchiectasis.**—Twelve patients with acquired bronchiectasis were treated with adequate amounts of sulfadiazine. Specimens of bronchial secretion were obtained by bronchoscopic aspirations at intervals from one to four days. By a special method, clear filtrates of the specimens were obtained and the concentration of sulfadiazine in the bronchial secretion was compared with the blood level of sulfadiazine obtained at the time of bronchoscopy. The average ratio of the concentration in the bronchial secretion to the one in the blood was 0.58 with an average variation from the mean of 14 per cent. In 10 patients with acquired bronchiectasis a 5 per cent suspension of microcrystalline sulfathiazole or a 2.5 per cent aqueous solution of sulfadiazine was instilled bronchoscopically or directly through the larynx. Specimens of the bronchial secretion were obtained by bronchoscopic aspiration at twenty-four-hour intervals. The concentrations found when microcrystalline sulfathiazole was used depended largely on the amount of sputum produced at the time of instillation. When aqueous solution of sulfadiazine was used only insignificant amounts of sulfadiazine were

found after twenty-four hours regardless of the amount of secretion. Ten patients received sulfadiazine by mouth in courses lasting from four to fifteen days. The blood level was kept between 8 and 12 mg. per cent. Bronchoscopic aspirations were performed during the same time. The clinical effect was estimated on the basis of the reduction in amount of expectoration and on the basis of alteration in the bacterial flora in the bronchoscopically obtained specimens. At the end of the combined course of sulfadiazine and bronchoscopic aspiration, the daily sputum volume was reduced to one-fifth to one-third of the original amount of sputum. Bacteriological studies of the specimens removed by bronchoscopic aspirations were not conclusive, since no uniform results were obtained. The instillation method has disadvantages, such as the irregular distribution of the material, the necessity of frequent instillation, the increase in viscosity of the sputum and the decrease in efficacy in the presence of purulent material. There was one untoward reaction following the instillation of 5 per cent microcrystalline sulfathiazole suspension which was probably due to transient occlusion of some segmental branch bronchi. The combined sulfonamide and bronchoscopic treatment should be of value in the preoperative treatment of suppurative pulmonary diseases. In cases of nonsurgical bronchiectasis it should be given a trial.—*Sulfonamides in Bronchial Secretion: The Effect of Sulfonamides in Bronchiectasis*, C. M. Norris, J. A. M. A., November 13, 1943, 123: 667.—(H. Abeles)

**Resection in Bronchiectasis.**—A series of 64 cases is presented (55 lobectomies, 9 pneumonectomies) with one operative death, giving a mortality of 1.6 per cent. All operations were of the one-stage type, using intratracheal anesthesia. Partial lobectomy of one or two lobes was done in some cases and individual ligation technique favored. The factors influencing morbidity and mortality are analyzed and divided into preoperative, operative and postoperative. Preoperative factors: (a) The most important is the degree and

distribution of the bronchiectatic involvement. If even a small amount of bronchiectatic tissue remains, especially on the involved side, the incidence of complication, especially empyema or atelectasis, is greater. (b) The degree of fibrosis and emphysema, especially in the older age group, is directly related to the degree of resistance to pulmonary infection and to factors involved in ventilation and circulation with possible resulting anoxia. The operative factors increasing morbidity and mortality are obstructed airway due to secretion or blood, inadequate pulmonary ventilation, reflex stimulation by surgeon and anesthetist, excessive trauma and blood loss, excessive physiological disturbances affecting the position of the mediastinum and preventing expansion of the remaining lobe or lobes. The postoperative factors include the retention of bronchial secretions, delayed expansion of the remaining lobe or lobes and anoxia. The author stresses the importance of overcoming each of the above conditions. The preoperative preparation should include adequate postural drainage and bronchoscopy to decrease the amount of secretion within the bronchi. A course of sulfa drug is of great value in lessening the degree of active infection. Anemia, hypoproteinemia and vitamin deficiency should be corrected. During operation, maintenance of a clear airway by the anesthetist is of paramount importance. By lessening the amount of secretion and blood, postoperative empyema and atelectasis are kept at a minimum. The removal of all involved tissue, careful hemostasis and avoidance of trauma, avoidance of reflex stimulation by excessive manipulation and adequate blood transfusions are routine considerations. Postoperatively, encouragement of cough and suction (by bronchoscopy if necessary or if in doubt) of retained secretions are indicated. Collapse of the remaining lobe is prevented by early aspiration of pneumothorax and closed drainage of empyema. Anoxia is best avoided by oxygen therapy and blood transfusions, both in adequate amounts. Of 59 cases with a sufficiently long follow-up period, the results were excellent or good in 42; 10 had residual

bronchiectasis with some cough or sputum, and, of these, 9 showed marked improvement; 4 had postoperative hemorrhages, but were otherwise in good condition; 2 had tuberculosis, one with occasional positive sputum after operation, the other had a contralateral spread which later cleared; one case had a residual empyema cavity due to delay in performing thoracoplasty. There were 2 late deaths, one due to pneumonia in the contralateral lung (also bronchiectatic), the other due to carcinoma of the main bronchus one year later. The complications after lobectomy (drainage was instituted in all 48 cases) were 5 instances of collapse of the remaining lobe, none permanent. In the 9 pneumonectomy cases, 7 required one or more thoracotomies (5 of these were drained immediately, at the time of operation) and 3 patients required thoracoplasty following drainage.—*Surgical Treatment of Bronchiectasis: Factors Influencing Post-operative Morbidity and Mortality*, H. C. Maier, *Surgery*, May, 1944, 15: 789.—(D. J. Rednor)

**Air Embolism following Bronchoscopy.**—Patient had extensive saccular and cylindrical bronchiectasis for which he was bronchoscoped about fifteen times during a period of two years. He experienced such marked relief from this treatment that lobectomy was not advised. At his sixteenth bronchoscopy no unusual difficulty was experienced, though slight bleeding was noted at the time, but this was presumed to be from superficial trauma to the mucous membranes. Convulsions beginning in the right leg and arm were noted one and three-quarters hours later. Ophthalmoscopic examination disclosed bubbles of air streaming through all vessels of the left retina and a smaller number in those of the right eye. Patient died in coma in another hour. At autopsy the diagnosis was confirmed and the source of the air embolism found in a small tear in a 2 mm. vein. Recommended prophylaxis is a head down position in any patient where bleeding is seen to occur after deep instrumentation of the bronchial passages.—*Death from Air Embolism following Bronchoscopy*, R. A. S.

Cory, J. *Thoracic Surg.*, February, 1944, 13: 30.—(W. M. G. Jones)

**Lobectomy for Bronchiectasis.**—Dissection of the hilum is preferred to the older method of tourniquet lobectomy. The advantages are avoidance of late infection of the stump, diminution of secondary hemorrhage, decrease of the chance of fistula formation and more complete removal of the diseased lobe. Out of a series of 100 consecutive patients, 8 died following operation. Two were late deaths due to tuberculosis and one of the remaining 6 deaths was due to tuberculous empyema. Only 2 deaths were due to suppurative bronchopneumonia and one was caused by brain abscess. Results were good in 83 cases, fair in 5 and poor in 4. Complications were few. The most common complication was postoperative atelectasis. The aim after operation is the immediate and permanent expansion of the remaining lobe or lobes, and when this takes place the result is almost invariably good. When expansion is not immediate, it may become complete within a few days or one week. When the delay is longer, complete expansion often fails to take place. Massive collapse occurred in 29 cases, 23 of which had eventually a good result. When the lung expands immediately, pulmonary complications are rare. Complete and immediate expansion occurred in 56 cases. The impression is gained that if adhesions are present over the remaining lobe, chances for complete reexpansion are better. Adhesions are therefore produced by a preliminary dusting of the good lobe by talcum powder. The high incidence of pulmonary tuberculosis following operation is striking. Seven cases developed this complication, and it proved fatal in 3. Dissection of the hilar structures may be the reason for this occurrence. Empyema developed in 55 cases, and in 47 it was certainly associated with bronchopleural fistula. In the remaining cases it was probably so. As long as the incidence of postoperative fistula remains necessarily high (because a perfect method of closure of the bronchial stump has not as yet been devised)

it seems advisable to drain all cases post-operatively for a short time. Of the cases who had a short period of postoperative drainage, up to five days, 76 per cent did not develop empyema, whereas only 56 per cent of the undrained cases remained uninfected.—*Dissection Lobectomy for Bronchiectasis*, T. H. Sellors & V. C. Thompson, *Lancet*, July 22, 1944, 247: 101.—(H. Marcus)

**Replacement of Protein Loss following Pulmonary Resection.**—To offset the great blood loss in major operations on the chest (White and Buxton found the average loss to approximate 725 cc. in thoracoplasty, 1,600 cc. in lobectomy, and 1,460 cc. in pneumonectomy), the authors have experimentally determined the need for replacement therapy and the optimum route of administration. Dogs were used, and determinations of the blood plasma protein fall due to anesthesia, exploratory thoracotomy and resection of lung tissue with and without complicating infection were made. The replacement therapy needed and the optimum route of administration were determined by giving blood transfusions, serum transfusions, serum intrapleurally and serum intrapleurally plus blood transfusions. In the control series (that is, without replacement), the lowering of plasma protein was found to be due to (1) the anesthesia (0.48 g. per cent average fall); (2) the operation on the chest wall (0.45 g. per cent average fall); (3) removal of lung tissue *per se* (1.5 g. per cent average fall in lobectomy, 1.31 g. per cent average fall in pneumonectomy with individual ligation); (4) infection (in most cases with infection, an even greater protein loss was noted). The replacement series of animals was divided into three groups, namely: (1) lobectomy, (2) pneumonectomy with mattress suture technique and (3) pneumonectomy with individual ligation. Lobectomy—those receiving serum replacement showed an average fall in plasma proteins of 0.58 g. per cent (1.5 g. per cent in the nonreplacement group). Those receiving whole blood replacement showed an average fall in plasma proteins of 0.63 g. per cent.

In both noninfected replacement groups alone the average loss was only 0.28 g. per cent. Pneumonectomy with mattress-suture technique—in this group, although the animals received only one-half as much replacement therapy as the preceding lobectomy group, a plasma protein level of 5.0 g. per cent or above was maintained in all the dogs (except the 2 receiving whole blood replacement). Pneumonectomy with individual ligation—the average fall with serum replacement was 0.56 g. per cent (compared with 1.31 g. per cent fall in the nonreplacement group); in the group receiving serum intrapleurally (heretofore serum replacement has been by the intravenous route only) the average fall was 1.0 g. per cent for the infected ones, and 0.79 g. per cent for the uninfected ones; if twice the amount of serum intrapleurally were given, the fall was 0.62 g. per cent in the infected group and 0.52 g. per cent in the noninfected group, showing the marked influence of sufficient replacement material; in the group receiving serum intrapleurally plus whole blood intravenously the average fall was 0.34 g. per cent for the infected group, and 0.44 g. per cent for the noninfected group. It is thus apparent that a marked fall in plasma proteins could be prevented by intravenous serum or whole blood in sufficient amounts. A similar result was obtained by the use of adequate amounts of serum intrapleurally. A greater fall was usually observed in infected animals (on the average, 25 per cent greater) than in the noninfected and could not be entirely prevented by replacement therapy, so that, while the level of plasma proteins was usually maintained above 5.0 g. per cent by replacement therapy, it was occasionally below this level in infected animals. The total amount of whole blood used to prevent hypoproteinemia was approximately 10 to 15 cc. per kilo of body weight. Larger amounts of serum intrapleurally were needed to obtain similar results. Clinical studies on humans show the same marked protein loss and the same response to intravenous blood or serum replacement. The authors stress the importance of maintaining the normal blood and

plasma protein levels in reducing the morbidity and mortality rates in chest surgery and also note the influence of hypoproteinemia on the development of postoperative infections (Cannon *et al.*). In civilian and military practice alike, they urge blood or serum transfusion before operation in the presence of a lowered plasma protein. Likewise, loss of additional protein during and following operation should be expected and adequate replacement planned for in advance, so that a normal or nearly normal plasma protein level can be maintained.—*The Use of Plasma for Filling the Pleural Space after Loss of Varying Amounts of Lung*, W. E. Adams & T. F. Thornton, *Surgery*, April, 1944, 15: 521.—(D. J. Rednor)

**Sulphamethazine in Pneumonia.**—The authors treated 77 cases of pneumonia with sulphamethazine. This sulphonamide is considered to be more soluble than sulphadiazine and, thus, its deposition in the kidneys is unlikely. Of the 51 bronchopneumonias treated in the under twelve group, 30 were secondary to measles, 2 to whooping-cough, and the rest primary. The ages varied from four weeks to eighty-five years. The dosage employed was 8 g. daily in six-hourly doses. Plenty of fluids were administered. Out of 77 patients, 65 appeared to respond and 12 did not; 3 of the latter died. Of those not responding, 6 cases in adults appeared to be aberrant cases of lobar pneumonia. The 3 deaths (4 per cent) occurred in (1) a thirteen-weeks-old baby with whooping-cough and bronchopneumonia, who was admitted on the sixth day and died four days later; (2) a case with measles and bronchopneumonia, admitted on the sixth day of disease, who died on the fifth day after admission; and (3) a twenty-six-year-old female with extensive bronchopneumonia, who survived only twelve hours after admission. Toxic effects occurred in only 3 cases. One child aged two showed almost complete sudden urinary suppression for one day. On stopping the drug the renal flow was restored within twenty-four hours. Two other patients under two developed a

curious painless brawny edema. All 3 children were acutely ill and all 3 made a good recovery. Apart from these toxic effects, sulphamethazine was extremely well taken. Vomiting was absent and nausea was present only slightly in 3 cases. There was no mental disturbance or depression and no interference with appetite. Cyanosis was only moderate. In a similar group of cases treated with sulphapyridine the mortality rate was 9 per cent.—*Pneumonia Treated with Sulphamethazine: Report of 77 Cases*, B. A. Peters & M. L. Easby, *Brit. M. J.*, August 21, 1943, 2: 230.—(D. H. Cohen)

**Bronchography in Unresolved Pneumonia.**—Forty patients with bronchiectasis were admitted to the station hospital at Fort Eustis, Virginia, during a period of fifteen months. Sixty-seven and five-tenths per cent of the patients in this series had an initial misdiagnosis of primary atypical pneumonia and subsequently were found to have pneumonitis around a preëxisting bronchiectasis. In 75 per cent of the patients the bronchiectasis was unilateral; in two-thirds of these it involved the lower lobe of the left lung. Bronchographic studies should be done in all cases of pneumonia which fail to resolve in a reasonable period (four to six weeks). (Author's Summary.)—*Importance of Bronchography in Cases of Unresolved Pneumonia*, G. S. Grier III, *Arch. Int. Med.*, June, 1944, 73: 444.—(G. C. Leiner)

**Obscured Pneumonic Densities.**—Two-thirds of the cardiac shadow lies on the left side of the thoracic spine and overlaps the mesial and lower portion of the left lung in the posterior-anterior view. In this view the cardiac density is fairly homogeneous and, therefore, any variation should arouse suspicion of pneumonia in this region. The fact that a pneumonic process may be obvious in the X-ray film does not rule out the possibility of another pneumonic lesion behind the heart. Recognition of such a lesion is important in the differential diagnosis of intrathoracic and intraabdominal disease and may prevent



needless operation. Illustrative is a patient who was admitted with a tentative diagnosis of acute appendicitis and in whom a pneumonic process was seen in the left lower lobe only in the oblique and lateral films. Meningeal irritation may also be of pneumococcal origin and may require multiple views for diagnosis. Four cases are described.—*Pneumonic Densities Obscured by the Cardiac Shadow*, G. H. Stein, *Radiology*, December, 1943, 41: 576.—(G. F. Mitchell)

**Atypical Pneumonia.**—The autopsy findings of 90 patients who died of atypical pneumonia are presented. The basic pulmonic lesion was an acute interstitial pneumonitis; its extent was from a portion of one lobe to a diffuse bilateral involvement. Slightly raised, whitish, firm, thickened bronchioles filled with pus were seen. They were bordered by a narrow zone of congested or hemorrhagic lung. In cases uncomplicated by secondary bacterial invasion there was no frank pulmonary consolidation. Microscopically the affected bronchioles showed ulceration of the mucous membrane. They were filled with pus, desquamated mucous membrane cells and mucoid fluid. The walls were edematous and infiltrated by plasma cells, lymphocytes and large monocytes. There was a peribronchiolar mononuclear cell exudate. The lung septa were edematous and contained mononuclear cells. Some alveolar spaces contained air, others edema fluid, others fibrinous cells, others masses of unorganized hemorrhage. No microorganisms were seen in the affected alveolar walls, alveolar lumina, peribronchiolar tissues, lung septa, bronchiolar walls. The larger bronchi showed edema, congestion and round-cell infiltration in the submucosa. Patches of fibrinous pleuritis were found in a few cases. In 4 cases cerebral lesions consisting of congested vessels and small perivascular hemorrhages were seen. Some hemorrhagic foci had necrotic centres, others, glial proliferations around them. The pulmonic lesions were similar to those observed in other virus diseases, such as experimental swine influenza, epidemic human influenza, measles

pneumonia. There was also a tendency toward secondary bacterial infection.—*Pathology of Atypical Pneumonia*, Abstract of paper by Major A. Golden, *Bull. U. S. Army Med. Dept.*, October, 1944, 81: 64.—(G. C. Leiner)

**Atypical Pneumonia.**—Primary atypical pneumonia has been defined by the Surgeon General as a syndrome characterized by an influenzal-like onset, relatively normal white count, relatively slow pulse, patchy areas of consolidation and absence of any proven bacterial etiology. Pathologically there is a hemorrhagic interstitial pneumonia with an acute bronchitis. Campbell *et al.*, from post-mortem observations, believe the mottled densities noted at X-ray examination are areas of atelectasis explainable on a mechanical basis. This study includes 79 patients with pulmonary lesions of the upper lung fields roentgenologically resembling pulmonary tuberculosis. All the patients were white, ranging in age from eighteen to forty-three years, with 76 per cent between eighteen and twenty-seven. Fifty-four had lesions of the right upper lobe, 24 of the left upper lobe and one of both upper lobes. They had the characteristic history and fever, but none had definite chills, pleuritic pains, dyspnea or cyanosis. None appeared acutely ill nor toxic. Seventeen of the patients had repeated sputum examinations by smear, but there were no facilities available for culture. The time for complete resolution was relatively rapid in most patients. The longest period for complete resolution was twenty-six days. The authors feel, after having studied over 1,000 cases of atypical pneumonia, that there is nothing pathognomonic in a single X-ray film to differentiate this entity from ordinary bronchopneumonia or tuberculosis. No case resembled lobar pneumonia nor had cavitation. Symptoms were frequently more severe with atypical pneumonia than with minimal tuberculosis. Seventy-seven per cent of this series presented symptoms of sufficient severity to warrant hospitalization without any knowledge of the pulmonary pathology.

The only positive differentiation between tuberculosis and atypical pneumonia is by the finding of a sputum positive for the tubercle bacillus and/or by serial X-ray study.—*Primary Atypical Pneumonia Simulating Infiltrative Pulmonary Tuberculosis*, A. L. Kruger, A. W. Wallace, J. P. Medelman & S. B. Grimes, *Dis. of Chest*, May-June, 1944, 10: 171.—(K. R. Boucot)

**Atypical Pneumonia.**—At Camp Crowder Station Hospital 40 cases of atypical pneumonia were observed which were different from other cases of atypical pneumonia. All the patients were members of one company and were admitted within ten days. Twenty-four healthy soldiers were X-rayed and in 4 of these the findings were similar to those in the hospital patients. The symptoms were malaise, chilliness, fever up to 104°F., dry cough and chest pain. In almost all cases the admission diagnosis was nasopharyngitis. Physical findings, such as harsh breath sounds or crepitant râles were present in few patients only. The leucocyte count was 5,000 to 11,000, the sedimentation rate was elevated. The sputa were negative for pneumococci and other pathogenic bacteria. X-ray examination showed increased hilar shadows and accentuated peribronchial markings and, a few days later, soft, irregular patchy mottling. Clinical improvement was seen usually after one week or ten days. Two patients showed patchy infiltrations on their chest roentgenograms even on the one hundred seventy-seventh day after admission. No fatalities occurred.—*Primary Atypical Pneumonia*, L. G. Idstrom & B. Rosenberg, *Bull. U. S. Army Med. Dept.*, October, 1944, 81: 88.—(G. C. Leiner)

**Atypical Pneumonia.**—A total of 1,862 cases of primary atypical pneumonia, etiology undetermined, were investigated. Bacteriological studies of the sputum, the white cell count, the X-ray appearance and the clinical course were used to distinguish the cases from 62 cases of pneumococcic lobar pneumonia occurring during the period of observation

at the same hospital. There was no death in the group of pneumococcic pneumonia, while in the series of primary atypical pneumonia 5 deaths occurred; one due to meningococcic meningitis developing in the convalescent period; in 2 cases gross invasion of hemolytic *Staphylococcus aureus* was found on autopsy. The chance of developing primary atypical pneumonia was greatest on about the twenty-fourth day following a soldier's admission to the camp, decreasing rapidly to about one-sixteenth of this chance on the thirty-fifth to fortieth day. This may be due to the increased strain during the period of admission to the camp or to the development of a specific immunity. By variation of the isolation technique it was found that no cross infection occurred between patients with upper respiratory infections and patients with primary atypical pneumonia. The minimum incubation period is probably seven days while the maximum incubation period is probably fifteen days. The onset of the disease was gradual in approximately two-thirds of this series while in the remaining one-third it was acute requiring early hospitalization. The most common constitutional symptoms were, in order of frequency, fever, malaise, chilliness; the most common symptoms of the respiratory tract were cough, sputum, chest pain; the most frequent physical findings were fever and dry râles. Since X-ray findings and localizing physical findings were frequently absent in the initial stage the diagnosis at the onset of the disease was often made by exclusion. For differential diagnostic purposes the sputum examination was most significant; the white cell count was usually normal or slightly elevated. No valuable information was obtained by the differential counts. The sedimentation rate ranged from 20 to 40 mm. per hour in the acute stage. With recurrences or reactivations, it showed secondary rises which were as significant as repeated X-ray examinations. The therapeutic measures consisted of expectorants, antipyretics, when indicated, and sulfadiazine when the temperature rose to 102°F. In a group treated by prolonged

bed-rest the incidence of recurrence was 2.6 per cent, while in a group treated by a conventional type of care the incidence of recurrence was 23.3 per cent. In spite of the prolonged period of bed-rest, the average period of hospitalization was shorter than in the comparison group. Following the period of bed-rest a program of physical reconditioning extending over twelve days was carried out. On the basis of these findings it is recommended to keep patients with atypical pneumonia at bed-rest until their sedimentation rate has decreased to at least 10 mm. in one-half hour. The average X-ray clearance time was 32.15 days in uncomplicated cases. The most common complications were effusions and bronchiectasis, some of the latter may have been present prior to the disease.—*Clinical Aspects of Primary Atypical Pneumonia: A Study Based on 1,862 Cases Seen at Station Hospital, Jefferson Barracks, Missouri, from June 1, 1942 to August 10, 1943, A. C. van Ravenswaay, G. C. Erickson, E. P. Reh, J. M. Siekierski, R. R. Pottash & B. Gumbiner, J. A. M. A., January 1, 1944, 124: 1.—(H. Abeles)*

**Cold Autohemagglutinins following Atypical Pneumonia.**—In a thirty-eight year old male patient atypical pneumonia was followed by the development of acrocyanosis following exposure to cold. This phenomenon could be reproduced at will by exposing the patient to cold. Capillaroscopy showed ballooning of the summit of the loops in the presence of cyanosis. The only blood abnormality was the presence of cold autohemagglutinins present even at room temperature. Patient's blood was of group O. His serum agglutinated not only his own washed red cells but also the washed red cells of normal group O persons. No hemoglobin was found in the urine at any time. Physical examination and laboratory studies gave no indication of the presence of other conditions in which cold agglutinins were previously described. It is assumed that by chilling reversible intravascular agglutination was caused by the autohemagglutinins. The possible hazard in using

convalescent blood from persons recovered from atypical pneumonia is pointed out.—*Cold Autohemagglutinins following Atypical Pneumonia Producing the Clinical Picture of Acrocyanosis, F. C. Helwig & E. D. Freis, J. A. M. A., November 16, 1943, 123: 626.—(H. Abeles)*

**Pseudobronchiectasis following Atypical Pneumonia.**—The authors point out that an acute, sometimes epidemic, atypical bronchopneumonia with leucopenia ("atypical pneumonia") may produce bronchial changes resembling bronchiectasis, but the damage to the bronchi is not permanent and recovery ensues in four to twelve weeks. The disease may be characterized as an acute respiratory infection marked by cough and thick purulent sputum, leucopenia (and negative laboratory studies, including those on the sputum), failure of sulfonamide therapy to relieve symptoms and gradual recovery within three months. X-ray films taken during the acute phase tend to show mottled densities and especially lobular or lobar atelectases. When the lesions are found in the upper part of the lung the X-ray films may resemble tuberculosis and, when in the basal portions, bronchiectasis. Lipiodol instillation may show short, wide, dilated bronchi, but these changes are not permanent and subsequent oil filling will be normal. The factors to be noted in the diagnosis to differentiate from bronchiectasis are: short clinical history; sputum which may be abundant or frankly purulent, but not foetid, nor does it separate into the usual three layers; bronchoscopic findings somewhat different from those of bronchiectasis. In the latter, edema and redness of the mucous membrane at the area of infection are usually found, but in pseudobronchiectasis the entire mucous membrane is edematous, a generalized suppurative bronchitis, superficial bleeding is rare, foetid odor is absent and relief from bronchoscopic treatment is minimal. Conservative treatment in such cases is indicated.—*Pseudobronchiectasis, B. Blades & D. J. Dugan, J. Thoracic Surg., February, 1944, 13: 40.—(W. M. G. Jones)*

**Pericarditis in Atypical Pneumonia.**—Three cases of pericarditis associated with primary atypical pneumonia are presented. The patients were between nineteen and twenty-seven years of age. The disease started with an upper respiratory infection which was followed by a pneumonia. Sputum examination for pneumococci, throat cultures for specific organisms and blood cultures were negative. Seven to forty-one days after the onset of the upper respiratory infection the patients developed rise in temperature, tachycardia and leucocytosis. A pericardial friction rub was heard in 2 of the cases, changes of the electrocardiogram typical of pericarditis were seen in all 3. X-ray examination revealed enlargement of the heart in one patient. It is believed that the cause of the pericarditis is identical with that of the primary atypical pneumonia. All patients recovered fully and all symptoms and signs of pericarditis disappeared.—*Pericarditis Associated with Primary Atypical Pneumonia, D. Finkelstein & M. J. Klainer, Am. Heart J., September, 1944, 28: 385.*—(G. C. Leiner)

**Rheumatic Pneumonia.**—Pathological examinations were performed on 63 consecutive cases of acute and chronic rheumatic fever. Of these, 8 showed distinctive pathological changes. Control cases included various types of acute pneumonia, chronic passive congestion of the lungs, both uncomplicated and complicated by pneumonia, and chronic organizing pneumonia. Rheumatic infection associated with specific pulmonary involvement gave sudden rise to a syndrome including fever, cough, bloody sputum and a leucocytosis usually over 15,000. Dyspnea was frequent and severe. There was little or no response to sulfonamide therapy and X-ray changes were not of specific diagnostic value. Pathological findings included fibrinous exudate more extensive and denser than in ordinary pneumonias, a focal necrosis and alveolitis consisting of a homogeneous eosinophilic swelling of the wall with necrosis and characteristic polymorphonuclear infiltration, fibrinoid swelling and cellular infiltration of

vessel walls sometimes extending to perivascular areas, varying degrees of infiltration with foamy mononuclear phagocytes, incomplete lining of alveolar walls with swollen septal cells, and finally specific granulomata termed "Masson bodies." These granulomata occurred in alveolar ducts with frequent extension into the alveoli resulting in varying degrees of atelectasis. They were round, oval or irregular bodies with pleomorphic cellular elements, few or no vessels, and partially or completely covered with cuboidal cells. Typical Aschoff cells were not found although the cellular components of the granulomata showed similar polarity and loose stroma. The "Masson body" was found in only a few instances in which no previous rheumatic history was elicited, one being a case of a seventy-three year old man dying of coronary sclerosis. Many of the granulomata appeared to originate as papillary protrusions from the walls of the alveolar ducts or alveoli, while others seemed to be formed by organization of fibrinous plugs. It is felt that the "Masson body" may remain a characteristic structure for an indefinite period.—*Rheumatic Pneumonia, K. T. Neuburger, E. F. Geever & E. K. Rutledge, Arch. Path., January, 1944, 37: 1.*—(D. G. Freiman)

**Pneumonia in Smallpox Contacts.**—An outbreak of pneumonitis followed the admission of a case of smallpox to a base hospital in the Middle East. Five medical officers and 2 nursing orderlies were affected, although they had been vaccinated recently and again after the patient was admitted, and all had shown immune reactions. The onset of the illness was malaise and fever between the eleventh and the eighteenth day after exposure. Fever lasted for from four to twelve days and reached 104°F. in some cases. A few crepitant râles were heard in the lungs. No characteristic laboratory findings were obtained. X-ray examination of the lungs showed mottled shadows which were rounded or confluent and were mainly present at the bases. Six of the 7 cases showed these findings. The X-ray lesions appeared on the third day after expo-

sure and in one case took six weeks to resolve completely. The conclusion was that the lesion observed represents some kind of virus pneumonia similar to lung lesions observed in other virus diseases. It may be that relatively immune close contacts react to the smallpox virus in this manner.—*Outbreak of Pneumonia in Smallpox Contacts*, H. T. Howat & W. M. Arnott, *Lancet*, September 2, 1944, 247: 312.—(H. Marcus)

**Inhalation Pneumonia.**—Acute inhalation pneumonias caused by noxious fumes are increasing in frequency, especially with the complexity and volume of wartime industry. Many industrial gases are potentially dangerous. Nitric fumes are discussed since they were the causative factor in the 2 cases reported by the authors. Nitric acid is used extensively in many industries, but ordinarily the concentration of the fumes is not sufficient to be toxic. However, accidents do occur resulting in the picture of severe acute pulmonary changes. If removed from the fumes, the patient may recover, or overwhelming edema may result in death. Nitric fumes consist of five oxides of nitrogen; the dioxides being considered the most insidious and the most toxic. Some also believe that nitrous gases make the body more sensitive to carbon monoxide and that a combination of factors is responsible in some reported deaths. Pathological changes in the lungs vary with the intensity of the exposure. There may be mild inflammation of the tracheobronchial mucosa or the irritation may be more extensive involving the minutest bronchioles, acute hyperemia and edema of tissues around the bronchioles giving a miliary or nodular appearance. A sterile bronchopneumonia may follow. In more severe cases a marked extravasation of fluid and pulmonary edema is found. If death occurs after an interval of a week or more, miliary fibrous nodules may be found at the terminal bronchi. Lung changes due to chronic inhalation have been reported among welders. The signs and symptoms of nitric fume inhalation are usually delayed from a few to as long as thirty hours, and,

consequently, cause and effect are not always apparent. The initial symptoms are headache, a sensation of pressure upon the anterior chest wall and dry cough which may be followed by chills, fever, respiratory distress and cyanosis. The acute illness or convalescence may be complicated by lobar or lobular pneumonia, recovery occurring after weeks of remissions. When the concentration has been high or exposure long, death usually occurs within forty-eight hours. When delayed, right heart failure, pleural effusion, pulmonary congestion and infection, anemia and focal hemorrhagic lesions in other organs play a rôle. While no chronic pulmonary disease has been proved as resulting from the effect of prolonged exposure to nitric fumes, anorexia, insomnia, weight loss, headache and dry cough are believed to occur. Roentgenograms are characterized by unusually extensive pseudo-nodular infiltrations throughout the lungs having no hilar or central preponderance. Subsequently, they become confluent, resembling patches of bronchopneumonia. In patients recovering, the roentgenograms are most striking, marked clearing being found in serial films taken only a few hours apart. Eventually the pseudo-nodular infiltrations disappear leaving only exaggerated lung markings, while in favorable cases no evidence of pulmonary change is visible after a period of four to ten days. Two cases of inhalation pneumonia from nitric fumes are presented. In the first case, they were produced by the open-vat mixing of nitric and hydrochloric acid, and the second case followed acetylene welding in the hold of a ship. Both had typical roentgenological findings and in both pulmonary clearing coincided with clinical improvement.—*Inhalation Pneumonia from Nitric Fumes*, M. C. Camiel & H. S. Berkan, *Radiology*, February, 1944, 42: 175.—(G. F. Mitchell)

**Loeffler's Syndrome.**—Loeffler's syndrome is a migratory transitory pulmonary infiltration demonstrable by X-ray and associated with eosinophilia. The extent of the radiographic findings and the level of eosinophilia

are frequently in startling contrast to normal physical findings, or signs consisting of a few moist and sibilant râles. The clinical course is mild and the symptoms minimal—fatigue, cough, occasional sharp chest pains, possibly small amounts of sputum, asthmatic attacks, and moderate temperature elevation. The roentgenogram reveals large or small consolidations appearing suddenly, disappearing and reappearing elsewhere. The lower lung fields are frequent sites, and the infiltrations may be sharply defined or vague in outline. The pathogenesis is not clear, but is usually considered to be on an allergic basis. Diagnosis rests on serial films demonstrating transitory shadows. Tuberculosis is the most important differential diagnosis, but coccidioides and neoplasms must also be considered. Treatment is not required in most cases. A case report is presented.—*Transitory Migratory Pulmonary Infiltrations Associated with Eosinophilia (Loeffler's Syndrome)*, J. W. Peabody, *Dis. of Chest*, September-October, 1944, 10: 391.—(K. R. Boucot)

**Loeffler's Syndrome.**—Among the differential diagnostic possibilities in lung lesions, Loeffler's syndrome has to be considered. This disease apparently has no common etiologic background. Allergy seems to play a rôle in some cases, while it cannot be demonstrated to do so in others. The clinical picture and course are quite characteristic. The physical signs are scant in relation to the amount of involvement, as demonstrated by X-ray. The eosinophilia is the most constant abnormal laboratory finding and ranges from 10 to 60 per cent. Cases have mainly been reported from Europe; a case reported in a Negress is given in this report.—*Eosinophilic Infiltration of the Lungs (Loeffler's Syndrome)*, S. H. Jones & C. R. Souders, *New England J. Med.*, September 7, 1944, 231: 356.—(H. Marcus)

**Tropical Eosinophilia.**—Loeffler's cases of pulmonary infiltrations with eosinophilia were all observed in Switzerland, and the disease was unknown outside of Europe. Tropical

eosinophilia was later described to occur in India, Palestine and Egypt, and although differences exist between the two diseases there are many similarities which makes one suspect a common etiology. The tropical disease is usually more severe and may become chronic, whereas Loeffler stressed the transient character of the syndrome. Since the original cases, however, others were observed where the duration was months and where patients were severely ill. The etiology of either disease is not known. An allergic background is postulated by some, contending that the allergen may be different in various patients and may vary with the locale. This etiology is disputed by others. A case report is appended of an Englishman who fell ill with a typical syndrome upon his return from India. He had an illness suggestive of this syndrome in India which was diagnosed as bronchitis. This illustrates the now well known fact that the disease may be acute, subacute or chronic, and subject to recurrences.—*Eosinophilia with Pulmonary Disease on Return from the Tropics*, J. Apley & G. H. Grant, *Lancet*, September 2, 1944, 247: 303.—(H. Marcus)

**Coccidioidomycosis.**—The fungus, *Coccidioides immitis*, is recognized as the etiologic agent in two definite entities: the chronic, progressive and highly fatal coccidioidal granuloma and the acute but more benign primary pulmonary coccidioidomycosis, endemic in certain regions of southwestern United States. The authors experienced an epidemic of 75 cases of the latter entity incident to military maneuvers in such an endemic area during the summer of 1942. Infections followed exposure to contaminated dust from the terrain, the incubation period averaging two weeks. Presumptive diagnosis was made on history of exposure with a symptomatology of thoracic pain, cough and occasional hemoptysis, chills and fever, cervical adenopathy with or without sore throat and, less frequently, arthritic pain. Thoracic physical signs were present in only about one-third of the cases and were usually minimal. The incidence of cutaneous manifestations,

erythema nodosum and/or erythema multiforme, was 25 per cent, considerably higher than in any other reported series. The white blood cell count ranged from normal to 29,000, while the differential count usually showed a late eosinophilia. Erythrocyte sedimentation rate was consistently elevated and its return to normal was considered a satisfactory indication of the patient's recovery. Positive cutaneous reactions to 1:100 or 1:1000 dilutions of coccidioidin were present in all cases. There was a 45 per cent incidence of reaction to tuberculin but careful routine sputum examinations revealed no tubercle bacilli. Hilar enlargement with accentuated bronchovascular markings in the involved parenchyma constituted the chief X-ray finding, although pleural effusion occurred in 3 instances and cavitation in an equal number. Culture of the fungus from the sputum and positive serological tests were the confirmatory diagnostic points. It was pointed out that a positive serological reaction is probably diagnostic but that a negative one does not exclude the infection since humoral antibodies may rapidly disappear. Also this test was believed to be a valuable prognostic guide, since primary infections show a high precipitin titre, gradually decreasing with improvement, and a low or absent complement fixation titre, while just the opposite is true in disseminated coccidioidal granuloma. Although the disease often ran a prolonged course of two or more months the prognosis was good in all save one case of associated coccidioidal granuloma of the skin. Treatment was symptomatic but there was some evidence that convalescent serum was beneficial in 2 cases. Finally it should be stressed that with the current flux of troops, bearing in mind the incubation period, pulmonary coccidioidomycosis may appear far afield from its endemic regions.—*Primary Pulmonary Coccidioidomycosis*, D. M. Goldstein & S. Louis, *War Med.*, September, 1943, 4: 299.—(L. R. Roll)

**Coccidioidomycosis.**—The follow-up report of 75 patients and the report of an additional 10 patients represent the largest series of

primary pulmonary coccidioidomycosis ever observed, diagnosed and treated. The 10 new patients acquired the disease in Pallen Pass, California, a hitherto not reported endemic area. Most of the inhabitants of the endemic areas have their primary infection during the first year of residence; only a few develop clinical symptoms usually called "valley fever," "desert fever" or "desert rheumatism." A certain number show an allergic response such as erythema nodosum. Primary pulmonary coccidioidomycosis has a high morbidity and a low mortality, coccidioidal granuloma has a mortality of 50 to 60 per cent. All patients returned to duty. In 3 patients cavity formation occurred, in 2 of them multiple cavities were present. The cavities closed spontaneously. Primary pleuritic effusion represented the initial infection in 3 patients. One of these 3 patients developed a pneumonic lesion which was followed by the appearance of two verrucous granulomata of the skin. They were removed by wide excision; no sinus formation or recurrence developed. Prior to the development of the skin lesions the blood precipitin and complement fixation tests had become positive. The general condition of this patient improved markedly following a whole-blood transfusion from a convalescent patient whose blood had a high precipitin titre without complement fixing antibodies. The most frequent symptoms were thoracic pain and cough, they were present in 88 per cent of the patients, chills occurred in 66 per cent, sore throat in 37 per cent, arthralgia in 28 per cent, hemoptysis in 18 per cent. Fever was a constant finding. Physical signs indicating involvement of the chest were present in 26 per cent of the patients. In the series of 75 patients erythema nodosum occurred in 19 per cent, erythema multiforme in 2.6 per cent; in the series of 10 patients a morbilliform rash of the trunk and lower extremities was noted in 4 patients. The skin lesions appeared eight to fourteen days after the incubation period which varied from one to three weeks. White blood cell count and differential count were of little diagnostic value, eosinophilia was highest

in the second or third week, averaging 6 to 8 per cent. The sedimentation rate was elevated. The Weltmann test was used in some cases as basis for the decision on further hospitalization. The tuberculin patch test was positive in 42 per cent which corresponds to the findings in the general population in that area. The coccidioidin skin test was positive in all patients. A positive serological test is diagnostic but a negative test does not necessarily rule out the infection. The complement fixation titre is high and the precipitin titre is low when dissemination of the granuloma occurs, in primary infections the opposite results are obtained. Sputum cultures for the fungus were often positive, but since the danger of infection is great this procedure should not be carried out routinely. The roentgenological findings were not characteristic, the most common findings were enlarged hilar shadows and increased pulmonary markings. Symptomatic conservative treatment is the method of choice. Convalescent blood with high precipitin titre was used twice and found to be of value. Sulfonamides were of no value.—*Primary Pulmonary Coccidioidomycosis: Follow-up of 75 Cases, with 10 More Cases from a New Endemic Area*, D. M. Goldstein & J. B. McDonald, J. A. M. A., February 26, 1944, 124: 557.—(H. Abeles)

**Monilliasis.**—Bronchopulmonary monilliasis is caused by *Monilia albicans*, a yeast-like fungus which belongs to the *imperfecta* group of fungi. *Monilia albicans* is widely distributed in the tropical and temperate climate. It is very resistant to drying. It is found as saphrophyte in the human mouth and discharges. This fungus is usually nonvirulent; however, when the resistance of the lining membranes of the bronchi or alveoli is lowered as in influenza, pneumonia or bronchitis, the inhalation of the fungus may cause disease. Three forms may be distinguished according to symptoms and course: the mild form with slight cough, scanty sputum and normal temperature; the moderate form with a pronounced cough, tenacious sputum and low grade fever; the severe form with dyspnea,

night sweats, cough, loss of weight and sticky sputum which has a sweetish or yeast-like odor. The important factors for the diagnosis are the laboratory tests which must include animal inoculation in order to prove the pathogenicity of the fungus. The production of lesions in the lungs of animals inoculated with the isolated monilias proves the virulence of the monilial strain. The roentgenographic examination reveals a process starting in the hilar regions and usually spreading along the pulmonary markings throughout both lungs offering a cotton-like appearance. The most effective treatment of mild and moderate cases consists of potassium iodide medication; the dose varies from 45 to 100 grains daily. Severe cases show little response to this treatment. Autogenous vaccine, X-ray treatment and sulfapyridine were also used. An additional case of bronchopulmonary monilliasis is reported. A thirty-four year old man was hospitalized for twenty days. He was discharged with the diagnosis of bronchitis. Six weeks later he was readmitted with the complaints of headache, dizziness, nonproductive cough and chest pains. The temperature ranged from 99°F. to 103°F. The radiological examination revealed mild hilar adenopathy and scattered cotton-like infiltrations throughout both lung fields. A diagnosis of bronchopneumonia was made and chemotherapy was instituted. Reexaminations during the following two weeks showed that the lesions were progressive and partly coalescent. On the sixteenth day of hospitalization the patient expectorated a large amount of sputum with yeast-like odor. *Monilia albicans* was demonstrated on smear and culture. Chemotherapy which had been ineffective was discontinued and the patient was put on 15 grains of sodium iodide intravenously and 10 drops of a saturated solution of potassium iodide by mouth every four hours daily. This was followed by a gradual drop in temperature and by resorption of the infiltrations. The patient was discharged on the eighty-ninth day of hospitalization. The chest film was normal except for slight fibrosis in both lung fields. Tubercle bacilli were



never recovered from the sputum; the tuberculin test was negative.—*Bronchopulmonary Moniliasis*, P. E. Wylie & J. A. DeBlase, J. A. M. A., June 17, 1944, 125: 463.—(H. Abeles)

**Chest Roentgenograms in Pertussis.**—Serial roentgenograms in the postero-anterior and right lateral positions were made on 222 children between the ages of five months and eight years. These children had been admitted to the Willard Parker Hospital, mostly ten to twenty-one days after the onset of symptoms. They were divided into three groups: an afebrile group, a group with low-grade fever and a group with fever over 101°F. for two or more days. The most frequent findings were homogeneous triangular shadows near the cardiophrenic angles and single or multiple opacities in any portion of the pulmonary field. Lateral views revealed frequent involvement of the right middle lobe. Evidence of pulmonary involvement occurred whether the clinical course was mild, moderate or severe. However, among patients with pulmonary consolidation, the percentage of those moderately or severely ill was high. Of the afebrile group, one-third showed increased markings and one-quarter pulmonary consolidation. The incidence of pulmonary infiltration was greater in patients who had fever, reaching 80 per cent in those with high fever. Lymphadenopathy was infrequent, especially in those with pulmonary consolidation. This finding was in keeping with the results found at autopsy. Hilar involvement was most frequent in those who showed no evidence of pulmonary consolidation. The authors believe that tenacious mucus and a narrow lobar bronchus contribute to the frequent atelectasis of the right middle lobe.—*Roentgenograms of the Chest Taken during Pertussis*, J. L. Kohn, I. Schwartz, J. Greenbaum & M. M. I. Daly, *Am. J. Dis. Child.*, June, 1944, 67: 463.—(K. R. Boucot)

**Acute Respiratory Conditions.**—The authors endeavor to demonstrate the reaction by African soldiers to respiratory diseases as

compared with the reaction of Europeans. The survey covers 1,250 admissions to the African Medical Division of an Army hospital. Three hundred and seventy-five of the admissions (30 per cent) were for respiratory infections. There were 76 cases of acute lobar pneumonia. Treatment was by oral administration of sulphapyridine and the response was more dramatic than in the European. However, in spite of the apparent rapid recovery, radiological examination proved that resolution was no quicker than in the European. The mean period of hospital stay was 21.8 days. There were 2 deaths. There were 12 cases of dry pleurisy with an onset of fever and chest pain and a dry rub on physical examination. No tuberculosis foci were seen on radiograms. There were 7 cases of pulmonary tuberculosis with positive sputum and definite lesions by radiogram. Six of the 7 had extensive exudative lesions with little evidence of restoration. Contrary to expectations, the incidence was found to be low and no case of "primary" tuberculosis was discovered. One case of lung abscess was admitted—he died within ten days of fulminating suppuration. There were 159 cases of bronchitis. They all responded to expectorants and inhalations and only required a few days in bed. The last group consisted of 67 cases of minor upper respiratory infections—coryza, pharyngitis, tracheitis and sinusitis. These were all admitted with a twenty-four-hour history of fever and responded well. The author concludes from this survey that there is clear evidence that the African is much more susceptible to acute respiratory infections in the Tropics than the Europeans. However, their response to treatment is uniformly good.—*An Analysis of Acute Respiratory Conditions in African Soldiers*, W. W. MacNaught & R. M. Murray-Lyon, *Brit. M. J.*, September 11, 1943, 2: 324.—(D. H. Cohen)

**Chronic Bronchitis.**—Noting the apparent high incidence of severe acute bronchitis with chronic features among military units in Panama, the author studied many such cases,

40 in detail. Only 4 of the 40 had previously had dusty occupations. Seventy per cent gave past histories of recurrent attacks of bronchitis characterized by cough with or without wheezing, occurring mainly in winter or with weather changes; many of these had experienced in addition sinusitis, hay fever and urticaria. One patient had suffered from severe sinusitis without bronchial involvement. The remainder gave no histories of previous bronchial or nasal disease. Among those with significant past histories there was almost a universal marked increase in severity and persistence of bronchial symptoms on arrival in Panama. Those without such histories developed symptoms within the first twenty-seven months, the average onset being one year after arrival. Symptoms are those of tracheobronchial irritation and of bronchiolar obstruction; they were more severe during damp weather and usually persisted throughout the patients' stay in Panama. Rhonchi were the commonest physical finding. Chest X-ray films typically were normal, save for increased basilar markings in 25 per cent. Bronchograms on 8 patients were not abnormal; and of 8 bronchoscopic examinations, 3 were normal and 5 showed bronchial mucosal thickening and edema and abundant secretions. Material for allergy studies was not available but a moderate eosinophilia was noted in 3 patients. Vigorous treatment of demonstrable possible causes rarely did more than lessen the signs and symptoms so that all 40 patients were eventually transferred from Panama. They could not, of course, be followed by the author, but he pointed out that previous experiences indicated 50 per cent of such cases usually improved on embarkation from the tropics with the remaining 50 per cent improving after reaching the United States, some recovering completely. From this study and others, the author concludes that primary chronic bronchitis is a clinical entity recognized in early stages as recurrent acute bronchitis, with successive attacks becoming more severe and prolonged until the final stage sets in when the patient is rarely free from symptoms. Emphysema often

results from it but bronchiectasis is a separate entity and not a sequel to bronchitis. He believes that predisposing factors are not well understood but may include exposure to dust, bronchial damage from previous acute infections, allergic conditions and chronic sinusitis. He believes further that in susceptible persons the most important precipitating factor is climate, particularly dampness.—*An Early Form of Chronic Bronchitis in Panama, A. G. Cohen, War Med., February, 1944, 5: 105.*—(L. R. Roll)

**Respiratory Tract Infections.**—In the first year of World War II the morbidity rate from respiratory infections caused by the hemolytic streptococcus increased markedly. The man-days loss in the Navy and the financial expenses for common diseases caused by the hemolytic streptococcus were high. A control program to check the dissemination of respiratory pathogens was instituted in several naval training stations in December, 1943. Comparable groups of untreated persons were observed for three months. In a camp with a severe, well advanced outbreak of streptococcal infections a prophylactic regimen of sulfadiazine 1 g. daily was instituted. It was followed by a rapid, contraseasonal decline in streptococcal infections and by a drop in incidence of rheumatic fever. Following the outbreak of a scarlet fever epidemic in another camp one-half of the complement was put on a prophylactic dose of 1 g. of sulfadiazine daily. The incidence of infection with hemolytic streptococcus, group A, type 19 which had caused the outbreak of scarlet fever was much lower in the group undergoing the prophylaxis. At a camp with complete turnover of personnel within short periods the incidence of respiratory infections in a group receiving 0.5 g. of sulfadiazine daily was much lower than in the control group. The only untoward effects of mass sulfadiazine prophylaxis were the occurrence of a drug rash in 0.5 per cent and serious constitutional disturbances, exfoliative dermatitis and agranulocytopenia, in 0.01 per cent of the entire group of 30,000 men. Drug fastness was not observed during the first four

months of the prophylaxis program.—*The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy*, A. F. Coburn, J. A. M. A., September 9, 1944, 126: 88.—(H. Abeles)

**Pulmonary Catarrh.**—The varying manifestations of recurrent nonspecific respiratory infection occurring especially in childhood allow for numerous names and diagnoses being given. Most of these numerous chronic or subacute infective pulmonary conditions could more satisfactorily be grouped together under the term "chronic pulmonary catarrh." The author found that, in 63 children under fourteen years of age referred to his asthma clinic, only 12 cases fit the picture of true allergic asthma—the remaining 51 were examples of chronic pulmonary catarrh. In a further series of 38 children seen in private practice, 33 showed evidence of recurrent catarrhal infections of the respiratory passages, only 5 being cases of true allergic asthma. The clinical features vary. In some children the attack is mild and is referred to as a bronchial cold with slight pyrexia and cough; in others the asthmatic features are predominant, with labored wheezy breathing and prolonged difficult expiration. In another group, a mild pneumonia attack seems to occur. The duration and termination also vary considerably, though the slowness of resolution and of disappearance of cough is most noticeable. The acute asthma picture often lasts several days and is followed by persistent wheezing and a cough, especially troublesome at night. Prolonged expiration is usual, but rapid shallow breathing is not uncommon. Râles and rhonchi may be heard anywhere, but especially posteriorly, and, significantly, they are almost always bilateral. Between attacks the child may be quite well, but one usually finds shallow breathing, poor development of the thorax as evidenced by round shoulders, flattening anteriorly and Harrison's sulcus, and coughing after deep breathing or exertion. Pharyngitis, large infected tonsils and postnasal catarrh may be seen. The latter conditions have been treated, but without the expected recovery.

Radiograms of the chest reveal unduly heavy lung roots with increased striations radiating from the hilar region, especially to the lower lobes. Bronchography shows normal bronchi. The differential diagnosis lies between pulmonary tuberculosis, bronchiectasis and true allergic asthma. Treatment in the acute attacks is that of acute bronchitis, asthma or pneumonia, depending on the predominant features. The important thing is to reduce the frequency of the attacks and to limit the permanent damage that may result. A warm, dry climate is beneficial. Breathing exercises are of extreme importance to correct faulty posture and movement of the thoracic cage, to promote diaphragmatic movement, to increase respiratory excursion and resilience, and to improve expiration. Group teaching for respiratory exercises is used with good results.—*Chronic Pulmonary Catarrh in Childhood*, A. B. Taylor, Brit. M. J., April 1, 1944, 1: 453.—(D. H. Cohen)

**Cold Vaccines.**—An attempt was made to evaluate the effect of cold vaccines on the incidence of the common cold. The preparations used were two vaccines for hypodermic use and three vaccines for oral use, all furnished by manufacturing pharmaceutical firms. There were three control groups. One was treated with placebos orally, one with placebos subcutaneously and one group remained untreated. The experiment was carried out on office and industrial workers of ages from nineteen to sixty-eight years on five different locations in the October to April period. Observations were made as to the number of colds, number of working days lost by each group, number of colds per person, number of days lost per person and number of days lost per cold. No evidence was found that any of the vaccines used offered clearly effective prophylaxis against either the frequency or the severity of the common cold.—*"Cold Vaccines" and the Incidence of the Common Cold*, L. C. McGee, J. E. Andes, C. A. Plume & S. H. Hinton, J. A. M. A., February 26, 1944, 124: 555.—(H. Abeles)

**Atelectasis in Poliomyelitis.**—Smith called attention to the fact that one-third of patients who had been in respirators and who were discharged to orthopedic hospitals and to convalescent homes died with infections of the respiratory tract, reported in records as bronchopneumonia. Coryllos and Birnbaum emphasized the rôle of atelectasis in the development of pneumonia. Factors predisposing to the development of atelectasis in poliomyelitis are reduction of vital capacity due to decreased tonus of skeletal muscles of the body as a whole, and impairment of the cough mechanism. Case reports are presented on 4 patients who developed atelectasis after the acute phase of poliomyelitis had been passed. Three of the 4 were still in the respirator. The fully developed pulmonary complication presented a critical picture characterized by fever, dyspnea, cyanosis, tachycardia, impaired cough reflex and prostration. These symptoms were due to pneumonia superimposed on a basis of atelectasis. X-ray evidence is presented. Prophylaxis suggested is avoidance of respiratory infection, the administration of sulfonamides at the earliest sign of such infection, the early use of bronchoscopy and the establishment as the criterion for removal from the respirator the ability to cough instead of the ability to breathe freely.—*Atelectasis Complicating Acute Poliomyelitis with Involvement of Respiratory Muscles*, M. Cooperstock, *Am. J. Dis. Child.*, June, 1944, 67: 457.—(K. R. Boucot)

**Multiple Echinococcus Cysts.**—Hydatid disease is most commonly encountered in areas where sheep pasturage prevails. Two cases of multiple echinococcus cysts are reported. The first case occurred in a sheep herder who

complained of shortness of breath and chest pain. A chest roentgenogram revealed a large shadow in each lung field. Both shadows proved to be caused by echinococcus cysts on operation. The cysts were removed without complication. A follow-up examination three years after the operation revealed a normal chest roentgenogram and no respiratory symptoms. The second case occurred in a school girl who had close contact with dogs. An intraabdominal echinococcus cyst was discovered at the occasion of an appendectomy. Subsequent examinations revealed a mass above the right diaphragm and abnormal contours of the spleen and of the liver as demonstrated with the aid of pneumoperitoneum. Several cysts of the liver and cysts closely attached to the uterus and to the spleen were removed through a thoracotomy and through a laparotomy at a later date. Several cysts of the liver had penetrated the diaphragm without invading the lung. They produced the supradiaphragmatic shadow on the chest film. The removal of the cysts was preceded by aspiration of about 30 to 50 cc. of the cyst fluid followed by injection of about 10 to 20 cc. of 10 per cent solution of formaldehyde. Then the contents of the cysts including the germinal layer were removed by suction. The wall of the cavity was wiped with the same solution and washed out with saline. Drainage or packing of the cavity is contraindicated, the remaining space may be filled with saline. Eosinophilia was not present in either case. The echinococcus skin test was positive in both patients; however, caution in its evaluation is advised since the test may be positive in the absence of hydatid disease.—*Multiple Echinococcus Cysts of the Lung, Liver and Abdomen*, E. Holman & P. Pierson, *J. A. M. A.*, April 1, 1944, 124: 955.—(H. Abeles)



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